SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Injectable Dermal Filler

Device Trade Name: *Restylane® Eyelight*

Device Procode: LMH

Applicant's Name and Address: Galderma Laboratories, L.P.
2001 Ross Ave Ste. 16
Dallas, TX 75201

Date of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P040024/S135

Date of FDA Notice of Approval: May 8, 2023

Priority Review: No

The original PMA (P040024) for *Restylane* was approved on March 25, 2005, and is indicated for mid-to-deep dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds (NLF). The PMA Supplement for *Restylane-L* (P040024/S039) was approved on January 29, 2010, and is indicated for mid-to-deep dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds; and for implantation into the deep dermis to superficial subcutis for the correction of moderate to severe facial folds and wrinkles, such as nasolabial folds, respectively. The PMA Supplement for *Restylane-L* (P040024/S056) was approved on August 30, 2012, and is indicated for mid-to-deep dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds; and for submucosal implantation for lip augmentation in patients over the age of 21. The SSEDs to support these indications are available on the CDRH website and are incorporated by reference herein.

Restylane-L, rebranded as *Restylane Eyelight* for this new indication is being submitted as a Panel-Track Supplement (P040024/S135) to the *Restylane* PMA (P040024). The study was performed in the US under IDE G190159 to establish a reasonable assurance of safety and effectiveness for the use of *Restylane Eyelight* for the improvement of infraorbital hollowing in patients over the age of 21.

II. INDICATIONS FOR USE

Restylane Eyelight is indicated for the improvement of infraorbital hollowing in patients over the age of 21.

III. CONTRAINDICATIONS

- *Restylane- Eyelight* is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.
- *Restylane Eyelight* contains trace amounts of gram-positive bacterial proteins and is contraindicated for patients with a history of allergies to such material.
- *Restylane Eyelight* contains lidocaine and is contraindicated for patients with a history of allergies to such material or other amide type anesthetics.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the *Restylane Eyelight* labeling.

V. DEVICE DESCRIPTION

Restylane Eyelight is a transparent, viscous, and sterile gel of hyaluronic acid (HA) generated by Streptococcus species of bacteria and chemically crosslinked with BDDE (1.4-butanediol diglycidyl ether). The gel is suspended in phosphate buffered saline pH 7 at a HA concentration of 20 mg/mL with 0.3% lidocaine.

Restylane Eyelight injectable gel is supplied in a disposable glass 1 mL syringe with a luer-lock fitting and it is co-packed with a sterilized needle as indicated on the carton (29 G x ½"). Restylane Eyelight can be injected using a 29 G x ½" needle or a 25 and 27 G x 1 ½" blunt tip cannula.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are other approved injectable gels and other procedures in the United States for correction of infraorbital hollowing, such as, fat grafting, implants, and surgery. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

Restylane-L is manufactured by Q-Med AB and was approved for marketing in the European

Union in January 2009. In January 2010, *Restylane-L* received US marketing approval (P040024/S039) for mid-to-deep dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds (NLF) in patients over the age of 21. *Restylane-L* has been approved for marketing in over 80 countries. It is estimated that over 60 million treatments with the Restylane family of products have been administered since original market introduction and none of the products in the family have been removed from the marketplace for any reasons related to safety, effectiveness, patient or physician complaint, or dissatisfaction.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential adverse effects (e.g., complications) associated with the use of the device, occurring in at least 1% of the subjects as reported in the clinical study include implant site swelling, headache, and implant site pain (with a frequency of less than 4%). Other adverse effects reported with less frequency (less than 2%) included: implant site bruising, implant site mass, and implant site edema. The adverse event reports received from post-marketing surveillance (from voluntary reporting and published literature) for the use of *Restylane Eyelight* with and without lidocaine for infraorbital hollowing in the U.S. and other countries most commonly included reports of transient swelling/edema and inflammatory reactions with immediate onset or delayed onset, up to several weeks after treatment.

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

- mass formation/induration
- erythema
- bruising/bleeding
- pain or tenderness
- discoloration/hyperpigmentation
- papules or nodules
- asymmetry/deformity
- short duration of effect
- presumptive bacterial infections and abscess formation including cellulitis and purulent discharge
- other injection site reactions and skin reactions including burning sensation, dryness, discomfort, exfoliation, irritation, and warmth
- eye disorders such as dry eye, eye swelling, increased lacrimation, eyelid ptosis, and

visual impairment including blurred vision and blindness

- hypersensitivity
- pruritus
- neurological symptoms including hypoesthesia, paraesthesia
- scarring
- ischemia and necrosis due to unintentional intravascular injection or embolization
- granuloma/foreign body reaction
- device dislocation
- rash
- discharge/extrusion of device
- urticaria
- blisters/vesicles
- dermatitis
- capillary disorders such as telangiectasia
- acne
- muscle twitching and muscle weakness
- encapsulation
- symptoms of reactivation of herpes infection
- dermatophytosis
- other dermatological events including dry skin and skin wrinkling
- non-dermatological events including malaise, headache, pyrexia, sinusitis

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

Reports of serious adverse events for *Restylane Eyelight* are rare. The most reported serious adverse events were infection/abscess, swelling, mass, hypersensitivity/allergic reactions, and ischemia/necrosis. Other concurrent serious events included: pain/tenderness, erythema, and bruising.

Serious infections/abscesses were mostly reported with a time to onset ranging from a few days up to 2 months following the injection. The infections usually resolved after three months and most of the patients had recovered or were recovering at the time of last contact. The treatments included: antibiotics, analgesics, and corticosteroids.

Serious swelling was mostly reported with a time to onset ranging from a day to a few months. Most of the patients had recovered or were recovering at the time of last contact. The treatments included; corticosteroids, antibiotics and hyaluronidase.

Serious mass was reported with a time to onset ranging from two weeks to a year. The outcome usually was recovered or recovering at the time of last contact. The treatments included: analgesics, antihistamine, antibiotics, corticosteroids and hyaluronidase.

The onset of serious hypersensitivity/allergic reactions generally varied from immediately to a few weeks post injection. The majority of the events were recovering or recovered at the time of last contact. The treatments included analgesics, antihistamine, antibiotics, and corticosteroids.

Vascular occlusion resulting in ischemia/necrosis and visual 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 embolization.

Isolated rare cases of ischemic events affecting the eye leading to visual loss, and the brain resulting in cerebral infarction, following facial aesthetic treatments have been reported. Reported treatments include anticoagulant, epinephrine, aspirin, hyaluronidase, steroid treatment, analgesics, antibiotics, local wound care, drainage, surgery and hyperbaric oxygen. 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.

Late-onset adverse events (greater than 2 years after injection with dermal fillers), such as delayed-onset inflammation or granulomas, in the infraorbital region following treatment with Restylane fillers have been reported in low numbers. Adverse events, such as puffiness, lumps,

or swelling, have resulted in negative cosmetic outcomes, but these events were noted as rare and can be correctable. Correcting these adverse events may involve additional treatment or interventions, such as further treatment injections to smooth out lumps or bumps, or the use of hyaluronidase. In some cases, time alone may allow the adverse event to resolve. It is important to note that the appropriate correction for each adverse event will depend on the nature and severity of the event, and should be determined on a case-by-case basis by a qualified healthcare professional

Delayed-onset inflammation near the site of dermal filler injections is one of the known adverse events associated with dermal fillers. Cases of delayed-onset inflammation have been reported to occur at the dermal filler treatment site following viral or bacterial illnesses or infections, vaccinations, or dental procedures. Typically, the reported inflammation was responsive to treatment or resolved on its own.

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

IX. SUMMARY OF NONCLINICAL 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.

C. Additional 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.

X. SUMMARY OF PRIMARY CLINICAL STUDY

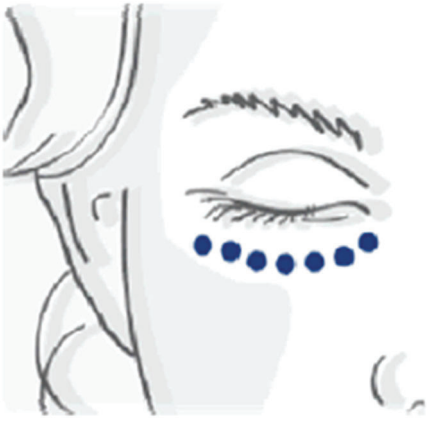
The applicant performed a clinical study (43USTT1904) to establish a reasonable assurance of safety and effectiveness for *Restylane Eyelight* for correction of infraorbital hollows in participants over the age of 21 in the US under IDE G190159. Data from this clinical study

were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Participants were treated between November 11, 2019 and October 20, 2021. The database for this Panel Track Supplement reflected data collected through April 06, 2022 and included 333 participants who were randomized and treated with either *Restylane Eyelight* (N = 287) or no treatment control (N = 46) at the outset of the study. There were 16 investigational sites.

The study was a multicenter, prospective, randomized, no-treatment controlled, evaluator-blinded study designed to evaluate the safety and effectiveness of *Restylane Eyelight* for correction of infraorbital hollows. Study participants were randomly assigned in a 6:1 ratio to treatment or no treatment control and followed for 12 months. At the Month 12 visit, all participants were offered an optional *Restylane Eyelight* treatment and were followed for an additional 6 months if treated. The Treating Investigators (TIs) could inject a maximum volume of 2 mL (1 mL per side) at each treatment visit into the supraperiosteal plane of the orbital rim. The infraorbital treatment area is defined as the junction of the lower eyelid and midface where a volume deficit had formed. The area is bordered by the nasal sidewall medially, the temporal region of the bony orbit laterally, the bulk of the lower eyelid superiorly, and the superior aspect of the mid-face inferiorly. Injection was permitted with a needle (co-packed 29 G x ½" thin wall) or a cannula (TSK Steriglide 25 G or 27 G x 1½").



1. <u>Clinical Inclusion and Exclusion Criteria</u>

Enrollment in the 43USTT1904 study was limited to subjects who met the following key inclusion criteria:

- Males or non-pregnant, non-breastfeeding females over the age of 21.

- Moderate or severe (Grade 2 or 3 on the Galderma Infraorbital Hollows Scale, GIHS) infraorbital hollows with no more than one grade difference between the left and right side at baseline as assessed by the blinded evaluator.
- Visual function assessment tests without findings according to treating investigator.
- Subjects who were willing to abstain from any other facial plastic surgical or cosmetic procedure(s) during the duration of the study (e.g., laser or chemical resurfacing, needling, facelift, radiofrequency).
- Subjects with the intent to undergo correction of both orbital hollows.
- Subjects who were willing to comply with the requirements of the study including being photographed, following post-treatment care instructions, completing the diary, attending all study visits and provided a signed written informed consent.

Subjects were <u>not</u> permitted to enroll in the 43USTT1904 study if they met any of the following key exclusion criteria:

- Known/previous allergy or hypersensitivity to any injectable hyaluronic acid (HA) gel or to gram positive bacterial proteins.
- Known/previous allergy or hypersensitivity to local anesthetics, e.g., lidocaine or other amide-type anesthetics.
- Active or a history of recurrent or chronic infraorbital edema or rosacea or uncontrolled severe seasonal allergies.
- Lower lid retraction or exophthalmos.
- Pigmentation abnormalities around the eyes and/or dark circles under the eyes due to pigmentation changes and not from infraorbital hollow shadowing.
- Ectropium, entropion, or trichiasis of the lower eyelid or eye diseases that lead to reddening and tendency of watering of the eye.
- Tendency to accumulate eyelid edema, had developed festoons, or had large and/or herniating infraorbital fat pads.

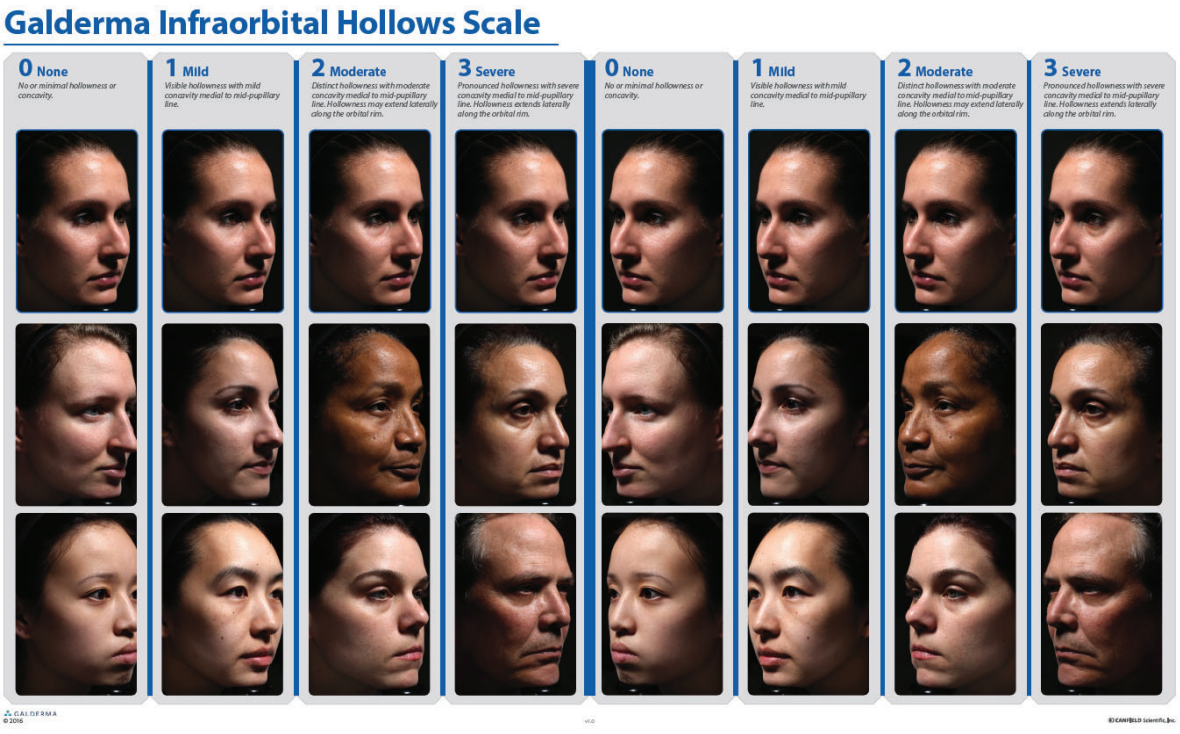
2. <u>Follow-up Schedule</u>

All study participants were scheduled to return for follow-up assessments at 1, 3, 6, 9, and 12 months after the baseline visit. Participants in the treatment group were offered optional touch-up treatment with *Restylane Eyelight* one month after initial treatment. Additional follow-up visits at 72 hours (telephone call), 14 days and 1 month were scheduled after each treatment.

All participants were offered treatment at the 12 months visit. Participants who received the optional 12-month treatment were scheduled for a follow-up by phone at 72 hours, and follow-up visits at 14 days, 1, 3, and 6 months after treatment. Vision assessments (Snellen visual acuity, extraocular muscle function, and confrontation visual field testing) were performed at the treatment visits before and after treatment, as well as 14 days after each treatment.

Pre- and post-procedure, the objective parameters measured during the study included the Blinded Evaluators' (BE) live assessment of the participants Infraorbital hollows using the validated 4-grade photographically based Galderma Infraorbital Hollows Scale (GIHS) performed for each infraorbital hollow separately. The 4 scores represent visibly distinct degrees of volume deficiency in the infraorbital areas of the face, where 0=None, 1=Mild, 2=Moderate, and 3=Severe (shown in **Figure 1**).

Figure 1: Galderma Infraorbital Hollows Scale



Other measures were the TIs' live assessments of the subject's improvement on the Global Aesthetic Improvement Scale (GAIS).

Study participants performed a self-assessment utilizing the GAIS, the validated FACE-Q™ Satisfaction with outcome module, and the Subject Satisfaction Questionnaire. Study

participants also reported when they felt comfortable returning to social engagement in the Subject Diaries. Additionally, the participants' diaries were used to collect information about injection related events after treatment. Adverse events and complications were recorded at all visits.

The key timepoints are shown below in the tables summarizing safety and effectiveness.

3. Clinical Endpoints

With regards to safety, paper subject diaries were used by the participants to record any pre-defined, expected injection related event (IRE) post-treatment during 28 days after each treatment. Participants were asked to assess each IRE as none, tolerable, affects daily activities, or disabling. AEs were evaluated by the TI at all visits.

With regards to effectiveness, the primary effectiveness measurement was the BEs' live assessment of the validated 4-grade photographically based GIHS performed separately for each infraorbital hollow, at 3 months after baseline. Secondary measurements included: BEs' GIHS assessment at further follow-up visits, the participants' and TIs' assessment of GAIS (Table 1), the participants' assessment of validated FACE-Q Satisfaction with outcome module questionnaire, the participants' assessment of the Subject Satisfaction Questionnaire, the participants' assessment for return to social engagement (from the Subject Diaries), and the Independent Photographic Reviewer's (IPRs) assessment of improvement from random pairings of baseline and post-baseline photographs.

Table 1: Global Aesthetic Improvement Scale (GAIS)

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

With regard to success/failure criteria, a responder was defined as a subject with at least 1 point

improvement in the GIHS score from baseline, on both sides of the face concurrently. Effectiveness of *Restylane Eyelight* was demonstrated if the responder rate at Month 3 for the treatment group was statistically significantly greater than for the no-treatment control group.

B. Accountability of PMA Cohort

At the time of database lock, data for all randomized 333 participants in the study were available for analysis. In total 380 participants were screened with 47 screen failures (12%). Of the 333 randomized participants, 245 were included in the modified Intention-to-Treat (mITT) population (all participants who had a month 3 visit conducted remotely were removed). A total of 316 participants were treated with *Restylane Eyelight*, 284 participants in the treatment group were treated at baseline and 32 of 45 participants (71%) in control group were treated at the 12-month visit. Out of the 284 participants treated at baseline, 221 participants (78%) opted for touch-up treatment and 164 (58%) opted for optional retreatment.

A summary of participant accountability is provided in Table 2, the analysis population in Table 3 and summary of treatment regimen for injected subjects is provided in Table 4.

Table 2: Summary of Participant Disposition

Category	Restylane Eyelight: Needle n (%)	Restylane Eyelight: Cannula n (%)	Restylane Eyelight n (%)	No Treatment n (%)	Overall n (%)
Screened					380
Screen failure					47
Randomized, N	148	139	287	46	333 (87.6)
Completed study	132 (89.2)	118 (84.9)	250 (87.1)	33 (71.7)	283 (85.0)
Did not complete study	16 (10.8)	21 (15.1)	37 (12.9)	13 (28.3)	50 (15.0)
Reason did not complete study					
Withdrew consent	8 (5.4)	7 (5.0)	15 (5.2)	6 (13.0)	21 (6.3)
Withdrew consent - COVID-19 related	0	2 (1.4)	2 (0.7)	1 (2.2)	3 (0.9)
Lost to follow-up	4 (2.7)	10 (7.2)	14 (4.9)	6 (13.0)	20 (6.0)
Other	4 (2.7)	2 (1.4)	6 (2.1)	0	6 (1.8)

COVID-19: coronavirus disease-19
Note: Denominator for percentage in the "randomized" row was based on the number of subjects screened; all other percentages were based on the intention-to-treat population.

Table 3: Analysis Populations

Study Population	Restylane Eyelight: Needle N	Restylane Eyelight: Cannula N	Restylane Eyelight N	No Treatment N	Overall N
Intention-to-treat population[1,2]	148	139	287	46	333
Modified intention-to-treat population[3]	113	97	210	35	245
Safety population[4]	146	138	284	45	329
Per-protocol population[5]	86	82	168	26	194

1. All subjects who were randomized at baseline and were analyzed according to the randomization scheme determined at baseline.
2. Includes four subjects randomized in error to *Restylane Eyelight* but not treated.
3. All subjects in the intention-to-treat population who did not have a GIHS Month 3 assessment conducted remotely at that visit.
4. All subjects who were treated with *Restylane Eyelight* or randomized to the control group and were analyzed according to the as-treated principle.
5. All subjects in the intention-to-treat population who completed 3 months after baseline visit without any deviations considered to have a substantial impact on the primary effectiveness endpoint.

Note: One subject was randomized to No Treatment and treated in error at baseline. In the intention-to-treat population, this subject is presented as "No Treatment". In the safety population, this subject is presented as "*Restylane Eyelight*: Cannula".

Table 4: Summary of Treatment Regimen for Injected Subjects

	Subjects	
	N	%
Initial Treatment – Baseline	284	100
Optional Month 1 touch-up	221	221/284 (78%)
Optional Month 12 retreatment	164	164/284 (58%)
Optional Month 12 treatment for control group	32	32/45 (71%)

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a pivotal study performed in the US. Participant demographics (age group, sex, ethnicity, and race) and baseline characteristics for the ITT population are presented in Table 5. Most of the participants were white (not Hispanic or Latino) females with a mean age of 44.4 years.

Table 5: Demographic and Baseline Characteristics (Intention-to-Treat Population)

Category	Restylane Eyelight: Needle (N=148)	Restylane Eyelight: Cannula (N=139)	Restylane Eyelight (N=287)	No Treatment (N=46)	Overall (N=333)
Age at baseline (years)					
Mean (standard deviation)	44.3 (12.15)	44.2 (10.98)	44.3 (11.58)	45.5 (12.27)	44.4 (11.67)
Median	45.0	45.0	45.0	45.0	45.0
Minimum, maximum	22, 73	24, 72	22, 73	24, 63	22, 73
Age category, n (%)					
22-29 years	21 (14.1)	12 (8.6)	33 (11.5)	8 (17.4)	41 (12.3)
30-44 years	51 (34.4)	55 (39.6)	106 (36.9)	14 (30.4)	120 (36.0)
45-59 years	58 (39.9)	62 (44.6)	120 (41.8)	17 (37.0)	137 (41.1)
60-73 years	18 (12.2)	10 (7.2)	28 (9.8)	7 (15.2)	35 (10.5)
Sex, n (%)					
Female	130 (87.8)	122 (87.8)	252 (87.8)	38 (82.6)	290 (87.1)
Male	18 (12.2)	17 (12.2)	35 (12.2)	8 (17.4)	43 (12.9)
Race, n (%)					
White	133 (89.9)	124 (89.2)	257 (89.5)	39 (84.8)	296 (88.9)
Black or African American	5 (3.4)	12 (8.6)	17 (5.9)	4 (8.7)	21 (6.3)
Asian	3 (2.0)	1 (0.7)	4 (1.4)	1 (2.2)	5 (1.5)
Native Hawaiian or Other Pacific Islander	0	1 (0.7)	1 (0.3)	0	1 (0.3)
Other	7 (4.7)	1 (0.7)	8 (2.8)	2 (4.3)	10 (3.0)
Ethnicity, n (%)					
Hispanic or Latino	40 (27.0)	26 (18.7)	66 (23.0)	9 (19.6)	75 (22.5)
Not Hispanic or Latino	108 (73.0)	113 (81.3)	221 (77.0)	37 (80.4)	258 (77.5)
Fitzpatrick skin type, n (%)					
I	1 (0.7)	4 (2.9)	5 (1.7)	0	5 (1.5)
II	43 (29.1)	32 (23.0)	75 (26.1)	11 (23.9)	86 (25.8)
III	53 (35.8)	64 (46.0)	117 (40.8)	20 (43.5)	137 (41.1)
IV	36 (24.3)	26 (18.7)	62 (21.6)	10 (21.7)	72 (21.6)
V	9 (6.1)	4 (2.9)	13 (4.5)	3 (6.5)	16 (4.8)
VI	6 (4.1)	9 (6.5)	15 (5.2)	2 (4.3)	17 (5.1)
Body mass index (kg/m^2)	n = 148	n = 137	n = 285	n = 46	n = 331
Mean (standard deviation)	25.56 (4.946)	25.03 (4.579)	25.30 (4.772)	25.98 (4.866)	25.40 (4.783)
Median	24.65	24.00	24.30	26.10	24.40
Minimum, maximum	17.7, 46.3	17.5, 40.7	17.5, 46.3	19.4, 42.5	17.5, 46.3
Blinded Evaluator GIHS score - left, n (%)					
0 (None)	0	0	0	0	0
1 (Mild)	0	0	0	0	0
2 (Moderate)	79 (53.4)	68 (48.9)	147 (51.2)	24 (52.2)	171 (51.4)
3 (Severe)	69 (46.6)	71 (51.1)	140 (48.8)	22 (47.8)	162 (48.6)
Blinded Evaluator GIHS score - right, n (%)					
0 (None)	0	0	0	0	0
1 (Mild)	0	0	0	0	0
2 (Moderate)	76 (51.4)	71 (51.1)	147 (51.2)	27 (58.7)	174 (52.3)
3 (Severe)	72 (48.6)	68 (48.9)	140 (48.8)	19 (41.3)	159 (47.7)

Note: Age and body mass index categories were determined by a median split of the intention-to-treat population age and body mass index, respectively.

For participants randomized to *Restylane Eyelight* treatment, the mean injected volume for both infraorbital hollows together was 1.34 mL (range 0.35 to 2.0) for the initial treatment. Optional touch-up was only available to subjects randomized to *Restylane Eyelight,* with a mean injected volume of 1.04 mL (range 0.15 to 2.00) for both infraorbital hollows together. The mean injected volume at optional retreatment at 12 months was 1.08 mL (range 0.20 to 2.00) for both infraorbital hollows together. For the participants randomized to no treatment control the mean injected volume at Month 12 was 1.47 mL (range 0.10 to 2.00) for both infraorbital hollows together.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the safety population cohort of 329 participants. The safety population included subjects who were treated with *Restylane Eyelight* or randomized to the control group. The key safety outcomes for this study are presented below. Adverse events are reported in Table 10.

Safety assessments such as visual acuity, confrontational visual fields, and ocular motility were evaluated at the screening visit and throughout the study.

- Snellen visual acuity assessments showed that over 97% of treatment group participants had no worsening (the same or better) of visual acuity from baseline to any of the study assessment timepoints. For the AEs of special interest (AESIs), 25 events of worsening on the Snellen visual acuity test were reported by 6% (19/316) of the treated subjects during the study. For 8 subjects (9 events) the visual acuity decline was maintained at the end of the study, with a maximum decline of a 2 line decrease from start to end of study. All the visual acuity changes were considered mild in intensity, and not related to the study product or injection procedure.
- All participants who received *Restylane Eyelight* had normal results on the extraocular muscle test at each visit.
- Confrontation visual field assessments showed no change in visual fields for all but one subject in the treatment group. The subject had, on Day 20 after initial treatment, a change in the visual field with an abnormal finding in the lower left of their right eye quadrant. This was considered mild in intensity, not related to study product or injection procedure, and resolved on Day 32. The subject had a normal finding in the lower left of their right eye quadrant at their next visit on Day 34.

Participants were asked to record pre-defined injection related events (IREs) of bruising, redness, pain (including burning), tenderness, lumps/bumps, itching, and swelling in a 28-Day paper subject diary after each treatment, and assess the level of intensity (i.e., none, tolerable, affects daily activities, or disabling). The most common pre-defined IRE were tenderness (89.7%), followed by swelling (85.0%). Pain (59.8%), bruising (63.1%), redness (61.5%), and lumps/bumps (53.5%) were also common. Subject's scores for the severity of these events are presented in Table 6 and durations are provided in Table 7. In general, the pre-defined IREs were tolerable and limited in time (with a duration of 7 days or less) after initial injection, touch-up injection, and retreatment injection.

Table 6: Pre-defined Injection Related Events (IREs) by Maximum Severity Occurring in Subjects After Injection (Safety Population)

	Tolerable m (%, m/n)	Affect Daily Activities m (%, m/n)	Disabling m (%, m/n)	Total n (%, n/N)
Post Initial Injection [1] (N=301)				
Pain (including burning)	164 (91.1)	14 (7.9)	2 (1.1)	180 (59.8)
Tenderness	255 (94.4)	14 (5.2)	1 (0.4)	270 (89.7)
Redness	164 (88.6)	20 (10.8)	1 (0.5)	185 (61.5)
Bruising	153 (80.5)	35 (18.4)	2 (1.1)	190 (63.1)
Swelling	207 (80.9)	47 (18.4)	2 (0.8)	256 (85.0)
Lumps/Bumps	139 (86.3)	21 (13.0)	1 (0.6)	161 (53.5)
Itching	42 (97.7)	1 (2.3)	0	43 (14.3)
Post-optional Touch-up Injection [1] (N=206)				
Pain (including burning)	98 (89.1)	12 (10.9)	0	110 (53.4)
Tenderness	152 (92.1)	13 (7.9)	0	165 (80.1)
Redness	110 (90.2)	11 (9.0)	1 (0.8)	122 (59.2)
Bruising	109 (86.5)	15 (11.9)	2 (1.6)	126 (61.2)
Swelling	141 (87.6)	18 (11.2)	2 (1.2)	161 (78.2)
Lumps/Bumps	85 (89.5)	10 (10.5)	0	95 (46.1)
Itching	24 (92.3)	2 (7.7)	0	26 (12.6)
Post-Retreatment Injection [1] (N=153)				
Pain (including burning)	77 (88.5)	10 (11.5)	0	87 (56.9)
Tenderness	111 (90.2)	12 (9.8)	0	123 (80.4)
Redness	72 (86.7)	11 (13.3)	0	83 (54.2)
Bruising	62 (77.5)	18 (22.5)	0	80 (52.3)
Swelling	97 (81.5)	20 (16.8)	2 (1.7)	119 (77.8)
Lumps/Bumps	65 (87.8)	9 (12.2)	0	74 (48.4)
Itching	22 (88.0)	3 (12.0)	0	25 (16.3)

[1] Number of subjects who completed at least one diary entry and were injected. n is the number of subjects reporting the IRE. m is the number of subjects reporting the severity.

Note 1: Percentages for symptom severity columns are based on the total number of subjects who reported 'Tolerable' or higher for a respective symptom in their subject diary; The total column percentages are based on the number of subjects who completed at least one diary entry and were injected.

Note 2: Maximum severity of both sides of the face is presented.

	Tolerable m (%, m/n)	Affect Daily Activities m (%, m/n)	Disabling m (%, m/n)	Total n (%, n/N)

Note 3: Initial treatment includes subjects randomized to Restylane Eyelight that received a baseline injection plus subjects randomized to No Treatment that had an optional initial treatment; Optional touch-up includes subjects randomized to Restylane Eyelight that received an optional touch-up at one month; Retreatment includes subjects randomized to Restylane Eyelight that received an optional retreatment at Month 12.

Table 7: Duration of Pre-defined Injection Related Events (IREs) [1] Occurring in Subjects After Injection (Safety Population)

	1 Day m (%, m/n)	**2 – 7 Days** m (%, m/n)	**8 – 13 Days** m (%, m/n)	**14 – 28 Days** m (%, m/n)
Post-Initial Injection [2] (N=288)				
Pain (including burning)	67 (37.2)	105 (58.3)	8 (4.4)	0
Tenderness	30 (11.1)	201 (74.4)	30 (11.1)	9 (3.3)
Redness	44 (23.8)	129 (69.7)	9 (4.9)	3 (1.6)
Bruising	24 (12.6)	105 (55.3)	45 (23.7)	16 (8.4)
Swelling	30 (11.7)	196 (76.6)	25 (9.8)	5 (2.0)
Lumps/Bumps	29 (18.0)	78 (48.4)	23 (14.3)	31 (19.3)
Itching	19 (44.2)	24 (55.8)	0	0
Post-Optional Touch-up Injection [2] (N=182)				
Pain (including burning)	37 (33.6)	67 (60.9)	4 (3.6)	2 (1.8)
Tenderness	17 (10.3)	130 (78.8)	12 (7.3)	6 (3.6)
Redness	35 (28.7)	76 (62.3)	6 (4.9)	5 (4.1)
Bruising	19 (15.1)	65 (51.6)	31 (24.6)	11 (8.7)
Swelling	24 (14.9)	108 (67.1)	17 (10.6)	12 (7.5)
Lumps/Bumps	14 (14.7)	50 (52.6)	15 (15.8)	16 (16.8)
Itching	10 (38.5)	15 (57.7)	1 (3.8)	0
Post-Retreatment Injection [2] (N=131)				
Pain (including burning)	24 (27.6)	58 (66.7)	5 (5.7)	0
Tenderness	19 (15.4)	85 (69.1)	14 (11.4)	5 (4.1)
Redness	26 (31.3)	48 (57.8)	7 (8.4)	2 (2.4)
Bruising	8 (10.0)	43 (53.8)	21 (26.3)	8 (10)
Swelling	15 (12.6)	86 (72.3)	12 (10.1)	6 (5.0)
Lumps/Bumps	10 (13.5)	45 (60.8)	11 (14.9)	8 (10.8)
Itching	14 (56.0)	11 (44.8)	0	0

[1] Number of days was defined as the sum of days when a sign/symptom was scored 'Tolerable' or higher, on either side of face. n is the number of subjects reporting the duration. n is the number of subjects reporting the IRE (Table 6). m is the number of subjects reporting within the timeframe.

	1 Day m (%, m/n)	**2 – 7 Days** m (%, m/n)	**8 – 13 Days** m (%, m/n)	**14 – 28 Days** m (%, m/n)

[2] Number of subjects who completed at least one diary entry and were injected when a sign/symptom was scored 'Tolerable' or higher.
Note 1: Percentages are based on the total number of subjects who reported 'Tolerable' or higher for a respective symptom in their subject diary.
Note 2: Initial treatment includes subjects randomized to Restylane Eyelight that received a baseline injection plus subjects randomized to No Treatment that had an optional initial treatment; Optional touch-up includes subjects randomized to Restylane Eyelight that received an optional touch-up at one month; Retreatment includes subjects randomized to Restylane Eyelight that received an optional retreatment at Month 12.

Adverse effects that occurred in the PMA clinical study:

Among the 316 treated participants, 40 (12.7%) participants experienced an AE considered related to study product or injection procedure after initial treatment (including touch-up treatment). Of the participants that were injected via needle, 8/163 (4.9%) experienced related AEs, and 32/153 (20.9%) of the participants injected via cannula experienced related AEs. Females and subjects with BMI less than or equal to 25.4 experienced more related side effects (Table 9). The percentage of participants who experienced related AEs was higher in participants who were injected at multiple depths (supraperiosteal and other) compared with participants who were injected supraperiosteally only, 29.2% and 11.3%, respectively. The percentage of participants who experienced related AEs was higher in participants who received local injection of anesthetics before treatment compared with participants who received topical anesthetics, 20.9% and 9.9%, respectively. All related AEs were mild or moderate in severity. Ten (3.2%) participants who received *Restylane Eyelight* experienced moderate events; all moderate events considered related to study product or injection procedure resolved by the end of the study. A summary of outcomes for AEs related to study product or injection procedure by injection method after initial treatment is presented in Table 10. Overall related AEs by preferred term and injection methods are presented in Table 10.

The most common related AEs (occurring in at least 1% of the subjects) after initial treatment were implant site swelling (3.8%), headache (2.2%), implant site pain (2.5%), implant site bruising (1.6%), implant site mass (1.3%), and implant site edema (1.3%). No subject experienced an AE leading to study withdrawal.

Four (1.3%) subjects who received *Restylane Eyelight* experienced SAEs, all considered unrelated to study product or injection procedure. Four (2.5%) participants injected via needle reported AEs of special interest (AESI), and thirteen (8.5%) participants injected via cannula. The visual disturbances, reported as AESIs, were considered mild in intensity and not related to study product or injection procedure. For two subjects the changes in vision met the reporting criteria to the Agency (Table 8). One subject experienced a light sensitivity in one eye that started 5 days after retreatment and lasted for 3 days before the event resolved, without any action taken. The event was considered mild in intensity and not related to study product or injection procedure.

Table 8: Changes in vision reported to the Agency

Description of event	Start Date End Date or Ongoing	Serious	Intensity	Relationship		Action Taken	Outcome	Time To Onset (Days)	Dura-tion (Days)
				Study Product	Injection Procedure				
Left and right eye, blurry vision*	15APR2020 28SEP2020	No	Mild	No	No	None	Resolved	56 after initial treatment	167
Transient change of visual field lower left quadrant for right eye	17AUG2020 29AUG2020	No	Mild	No	No	Visual field test	Resolved	19 after initial treatment	13

*Note: Diabetes mellitus was confirmed as the likely underlying cause of the event.

Table 9: Related AEs per sex and BMI subgroups

Subgroup		Subjects with related AEs after initial treatment including touch-up treatment (%, n/N)
Sex	Female (N=276)	40 (14.5%)
	Male (N=40)	3 (7.5%)
Body Mass Index (BMI)	BMI <= 24.25 (N=154)	28 (18.2%)
	BMI > 24.25 (N=161)	15 (9.3%)

Table 10 Summary of Outcomes for Adverse Events Related to Study Product or Injection Procedure by Injection Method: Initial Treatment

			Restylane Eyelight: Needle (N=163)		Restylane Eyelight: Cannula (N=153)		Restylane Eyelight: (N=316)	
Outcome	**Measurement**	**Statistics**	**Subjects**	**Events**	**Subjects**	**Events**	**Subjects**	**Events**
Adverse Event Type	Related	n (%)	8 (4.9)	11	32 (20.9)	59	40 (12.7)	70
Action taken	None	n (%)	6 (3.7%)	8	20 (13.1%)	32	26 (8.2%)	40
	Medication Treatment	n (%)	2 (1.2%)	3	11 (7.2%)	26	13 (4.1%)	29
	Non-pharmacological Treatment or Other Procedures/Test	n (%)	0	0	1 (0.7%)	1	1 (0.3%)	1
	Subject Withdrawn	n (%)	0	0	0	0	0	0
Severity of Related AEs	Mild	n (%)	8 (4.9)	11	26 (17.0)	43	34 (10.8)	54
	Moderate	n (%)	0	0	10 (6.5)	16	10 (3.2)	16
	Severe	n (%)	0	0	0	0	0	0
Number of Days to Onset of Related AEs	Any AE	n	NA	11	NA	59	NA	70
		Mean (SD)	NA	47.2 (96.38)	NA	31.2 (64.35)	NA	33.7 (69.73)
		Median	NA	1.0	NA	2.0	NA	2.0
		Min, Max	NA	0, 254	NA	0, 229	NA	0, 254
Duration of Related AEs	Any AE	n	NA	11	NA	56	NA	67
		Mean (SD)	NA	138.3 (143.02)	NA	20.7 (47.36)	NA	40.0 (83.02)
		Median	NA	79.0	NA	4.0	NA	4.0
		Min, Max	NA	1, 311	NA	1, 338	NA	1, 338

Table 11: Overall Related Adverse Events by Preferred Term and Injection Method: Initial Treatment (Safety Population)

System Organ Class Preferred Term	Restylane Eyelight: Needle (N=163) Participants n (%, n/N)	Restylane Eyelight: Cannula (N=153) Participants n (%, n/N)	Restylane Eyelight: (N=316) Participants n (%, n/N)
Implant site swelling	4 (2.5)	8 (5.2)	12 (3.8)
Implant site pain	0	8 (5.2)	8 (2.5)
Implant site bruising	1 (0.6)	4 (2.6)	5 (1.6)
Implant site mass	2 (1.2)	2 (1.3)	4 (1.3)
Implant site oedema	0	4 (2.6)	4 (1.3)
Implant site pruritus	0	2 (1.3)	2 (0.6)
Implant site discoloration	0	1 (0.7)	1 (0.3)
Implant site induration	0	1 (0.7)	1 (0.3)
Implant site paraesthesia	0	1 (0.7)	1 (0.3)
Headache	1 (0.6)	6 (3.9)	7 (2.2)
Hypoaesthesia	0	1 (0.7)	1 (0.3)
Syncope	0	1 (0.7)	1 (0.3)
Post inflammatory pigmentation change	0	1 (0.7)	1 (0.3)
Skin discoloration	1 (0.6)	0	1 (0.3)
Skin hyperpigmentation	0	1 (0.7)	1 (0.3)
Telangiectasia	0	1 (0.7)	1 (0.3)
Immunization reaction	0	1 (0.7)	1 (0.3)
Contusion	0	1 (0.7)	1 (0.3)

Note: Initial treatment included adverse events from subjects randomized to *Restylane Eyelight* that started on/after their baseline injection up until their optional retreatment, plus adverse events from subjects randomized to no treatment that started on/after their optional initial treatment. Adverse events were coded using the Medical Dictionary for Regulatory Activities Version 23.0. Related to study product or injection procedure = reasonable possibility. Percentages were calculated using the total number of subjects in the safety population as the denominator.

In the clinical study, 8 participants experienced in total 18 related AEs with an onset after 21 days. All of these AEs, except for one subject (mild implant site swelling on both sides, occurring after 24 days from treatment), were resolved during the study. Seven of the AEs resolved within less than 3 days, and in total 10 AEs resolved within 13 days. Six AEs were resolved after more than 14 days. Two participants experienced in total 3 AEs with moderate intensity (implant site edema and implant site swelling on left and right side), all others were of mild intensity. Medication was given for 12 of the AEs. Five participants with swelling were treated with either antihistamine, decongestant, penicillin, cortisone, hyaluronidase or other (eye cream), and one of the subjects was also treated with anti-inflammatory for pain. For one of the participants the related AE occurred after retreatment, for all the other

participants the AEs occurred after initial or touch-up treatment. There were no subjects with related SAEs in the study. One subject died due to COVID-19 during the study. No participant experienced an AE leading to study withdrawal.

2. Effectiveness Results

The analysis of primary effectiveness was based on the mITT population of 245 subjects at the 3-month time point. The analyses of secondary effectiveness were based on the ITT population (N=333). Key effectiveness outcomes are presented in Table 12, Table 13, Table 14, Table 15, and Table 16.

Primary Effectiveness Results

Restylane Eyelight provided a clinically and statistically significant improvement in the correction of volume deficit in the infraorbital hollows compared to the no-treatment control group. The primary effectiveness objective was met in that the treatment group responder rate was 87.4% which was statistically greater ($p < 0.001$) than the no-treatment control group with responder rate 17.7%, thus demonstrating superiority of *Restylane Eyelight* to no treatment. The difference in responder rates at Month 3 was 69.7%. Results were similar for the PP population. Responder rates are summarized in Table 12.

Table 12: Responder Rates Based on GIHS as Assessed by the Blinded Evaluator at Month 3 (mITT, Multiple Imputation)

	Restylane Eyelight N=210	No Treatment N=35	Difference	P-value
Responder rate, n (%)	184 (87.4%)	6 (17.7%)	69.7%	
95% CI	(81.73, 93.13)	(3.21, 32.22)	(52.54, 86.89)	<0.001

Note 1: 95% CI for Responder Rates and Difference is calculated using the Normal Approximation (Wald) method.
Note 2: P-Value is from the Cochran-Mantel-Haenszel test stratified by injection tool.

Secondary Effectiveness Results

The secondary effectiveness endpoint for responder rates at Months 6, 9, and 12, based on the blinded evaluators' (BEs') live assessments of the GIHS, were compared between *Restylane Eyelight* to no treatment. Statistical significance was achieved at all timepoints demonstrating a superiority of *Restylane Eyelight* (range: 63.5% to 86.0%) to no treatment (range: 11.1% to 13.5%). Participants that received optional treatment at month 12 were analyzed for responder rates at Months 3 and 6 after the optional treatment, based on the BEs' live assessment. For the *Restylane Eyelight* group the responder rate at Months 3 and 6 after

the optional treatment were 87.1% and 80.3%, respectively, and in the no treatment control group 82.8% and 65.5%, respectively (Table 13).

Table 13: Responder Rates Based on GIHS as Assessed by the Blinded Evaluator at Months 6, 9, and 12 (ITT, Observed Cases)

	Restylane Eyelight N=287	No Treatment N=46	Difference
Month 6			
Responder rate, m/n (%)	221/257 (86.0)	5/37 (13.5)	72.5%
95% CI	(81.75, 90.24)	(2.50, 24.53)	(60.67, 84.28)
Month 9			
Responder rate, m/n (%)	197/254 (77.6)	4/36 (11.1)	66.4%
95% CI	(72.43, 82.69)	(0.85, 21.38)	(54.97, 77.92)
Month 12			
Responder rate, m/n (%)	162/255 (63.5)	4/36 (11.1)	52.4%
95% CI	(57.62, 69.44)	(0.85, 21.38)	(40.57, 64.26)
Month 3 after Optional Treatment			
Responder rate, m/n (%)	135/155 (87.1)	24/29 (82.8)	
95% CI	(81.82, 92.37)	(69.01, 96.51)	
Month 6 after Optional Treatment			
Responder rate, m/n (%)	126/157 (80.3)	19/29 (65.5)	
95% CI	(74.03, 86.48)	(48.22, 82.82)	

Note 1: Difference = *Restylane Eyelight* responder rate – no treatment responder rate (where difference >0 indicated a higher percentage of responders in the *Restylane Eyelight* group).
Note 2: 95% confidence interval for responder rate and difference was calculated using the normal approximation (Wald) method.
Note 3: 95% confidence interval is not adjusted for multiplicity. It is for descriptive purposes only
Note 4: Only subjects who received a retreatment or optional initial treatment (for no treatment subjects) had visits at Month 3 and Month 6 after Optional Treatment.
Note 5: For m/n, m = number of subjects who met the criterion and n = number of subjects with non-missing assessment.
Note 6: The responder rate was defined as the number and percentage of subjects with at least a 1-point improvement from baseline on the GIHS, on both sides of the face, concurrently.

The secondary effectiveness endpoint proportion of subjects having at least "Improved" on the Global Aesthetic Improvement Scale (GAIS), as assessed live by the Subject and Treating Investigator separately, demonstrated higher improvement rate in the *Restylane Eyelight* group than in the No Treatment group at each visit up until optional treatment at Month 12. Results were summarized using dichotomized categories for the timepoints: Months 3, 6, 9, and 12. Subject and Investigator evaluations yielded similar results at most timepoints. Subject and Investigator evaluations of improvement are presented in Table 14 and Table 15.

From Month 1 through Month 12, aesthetic improvement as assessed on the subject GAIS ranged from 79.8% to 99.0% in subjects who received *Restylane Eyelight* compared with 0% to 2.9% in the no treatment control group (Table 14). Responder rates were generally similar between the *Restylane Eyelight* and no treatment control groups at Months 1, 3, and 6 after optional treatment.

From Month 1 through Month 12, aesthetic improvement as assessed on the Treating Investigator GAIS ranged from 87.5% to 99.5% in subjects who received *Restylane Eyelight* compared with 2.8% to 10.8% in the no treatment control group (Table 15). Responder rates were generally similar between the *Restylane Eyelight* and no treatment control groups at Months 1, 3, and 6 after optional treatment.

Table 14: Responder Rate Based on the GAIS at Each Visit as Determined by the Subject (Observed Cases) (Intention-to-Treat Population)

Statistic	Restylane Eyelight: Needle (N=148)	Restylane Eyelight: Cannula (N=139)	Restylane Eyelight (N=287)	No Treatment (N=46)
Month 1				
Responder rate, m/n (%)	133/139 (95.7)	120/133 (90.2)	253/272 (93.0)	1/35 (2.9)
Month 1 after Touch-up				
Responder rate, m/n (%)	104/105 (99.0)	92/93 (98.9)	196/198 (99.0)	NA
Month 3				
Responder rate, m/n (%)	126/130 (96.9)	119/128 (93.0)	245/258 (95.0)	1/38 (2.6)
Month 6				
Responder rate, m/n (%)	127/135 (94.1)	109/122 (89.3)	236/257 (91.8)	0/37
Month 9				
Responder rate, m/n (%)	125/137 (91.2)	98/116 (84.5)	223/253 (88.1)	0/36
Month 12				
Responder rate, m/n (%)	111/134 (82.8)	94/123 (76.4)	205/257 (79.8)	1/36 (2.8)
Month 1 after Optional Treatment				
Responder rate, m/n (%)	86/87 (98.9)	67/68 (98.5)	153/155 (98.7)	30/32 (93.8)
Month 3 after Optional Treatment				
Responder rate, n/N (%)	83/86 (96.5)	65/71 (91.5)	148/157 (94.3)	26/29 (89.7)
Month 6 after Optional Treatment				
Responder rate, m/n (%)	82/86 (95.3)	65/72 (90.3)	147/158 (93.0)	24/29 (82.8)

Note: For m/n, m = number of subjects who met the criterion and n = number of subjects with non-missing assessment. A responder was defined as a subject who responded as “improved”, “much improved”, or “very much improved” on the subject GAIS. No treatment subjects did not have a visit at Month 1 after touch-up. Only subjects who received a retreatment or optional initial treatment (for no treatment subjects) at month 12 had visits at Months 1, 3 and 6 after optional treatment.

Table 15: Responder Rate Based on the GAIS at Each Visit as Determined by the Treating Investigator (Observed Cases) (Intention-to-Treat Population)

Statistic	Restylane Eyelight: Needle (N=148)	Restylane Eyelight: Cannula (N=139)	Restylane Eyelight (N=287)	No Treatment (N=46)
Month 1 Responder rate, m/n (%)	131/137 (95.6)	133/134 (99.3)	264/271 (97.4)	1/35 (2.9)
Month 1 after Touch-up Responder rate, m/n (%)	103/104 (99.0)	95/95 (100)	198/199 (99.5)	NA
Month 3 Responder rate, m/n (%)	125/128 (97.7)	126/129 (97.7)	251/257 (97.7)	2/39 (5.1)
Month 6 Responder rate, m/n (%)	132/135 (97.8)	113/122 (92.6)	245/257 (95.3)	4/37 (10.8)
Month 9 Responder rate, m/n (%)	132/137 (96.4)	104/118 (88.1)	236/255 (92.5)	2/36 (5.6)
Month 12 Responder rate, m/n (%)	123/134 (91.8)	102/123 (82.8)	225/257 (87.5)	1/36 (2.8)
Month 1 after Optional Treatment Responder rate, m/n (%)	87/87 (100)	68/68 (100)	155/155 (100)	32/32 (100)
Month 3 after Optional Treatment Responder rate, m/n (%)	85/86 (98.8)	67/70 (95.7)	152/156 (97.4)	28/29 (96.6)
Month 6 after Optional Treatment Responder rate, m/n (%)	85/86 (98.8)	72/72 (100)	157/158 (99.4)	26/29 (89.7)

Note: For m/n, m = number of subjects who met the criterion and n = number of subjects with non-missing assessment. A responder was defined as a subject who responded as “improved”, “much improved”, or “very much improved” on the Treating Investigator GAIS. No treatment subjects did not have a visit at Month 1 after touch-up. Only subjects who received a retreatment or optional initial treatment (for no treatment subjects) had visits at Months 1, 3 and 6 after optional treatment.

For the secondary effectiveness endpoint FACE-Q Satisfaction with Outcome, showed that there were high Satisfaction with Outcome throughout the study from Month 1 through Month 12 for participants in the *Restylane Eyelight* (range 64.3 to 73.5) group compared to the no treatment group (range 14.1 to 16.2) (Table 16). FACE-Q satisfaction with outcome Rasch-transformed total scores were similar between the *Restylane Eyelight* and no treatment control groups at Months 3 and 6 after optional treatment.

Table 16: Summary of FACE-Q Satisfaction with Outcome Rasch-Transformed Total Scores at Each Visit (Observed Cases) (Intention-to-Treat Population)

Timepoint	Statistic	Restylane Eyelight: Needle (N=148)	Restylane Eyelight: Cannula (N=139)	Restylane Eyelight (N=287)	No Treatment (N=46)
Month 1	n	139	134	273	33
	Mean (SD)	71.1 (20.95)	66.6 (26.00)	68.9 (23.63)	14.7 (20.76)
	Median	68.0	68.0	68.0	0
	Minimum, maximum	0, 100	0, 100	0, 100	0, 59
Month 3	n	130	128	258	36
	Mean (SD)	76.8 (20.40)	70.1 (24.90)	73.5 (22.94)	16.2 (22.82)
	Median	79.0	73.0	79.0	0
	Minimum, maximum	0, 100	0, 100	0, 100	0, 63
Month 6	n	135	123	258	35
	Mean (SD)	73.6 (19.42)	68.9 (25.40)	71.4 (22.54)	15.4 (25.03)
	Median	73.0	73.0	73.0	0
	Minimum, maximum	24, 100	0, 100	0, 100	0, 100
Month 9	n	136	116	252	35
	Mean (SD)	69.6 (24.52)	65.1 (27.38)	67.5 (25.92)	14.6 (25.21)
	Median	73.0	63.0	68.0	0
	Minimum, maximum	0, 100	0, 100	0, 100	0, 100
Month 12	n	134	123	257	34
	Mean (SD)	65.6 (24.01)	62.9 (27.84)	64.3 (25.90)	14.1 (20.84)
	Median	63.0	59.0	63.0	0
	Minimum, maximum	0, 100	0, 100	0, 100	0, 63
Month 3 After Optional Treatment	n	86	71	157	29
	Mean (SD)	75.6 (20.02)	69.4 (23.15)	72.8 (21.64)	64.1 (22.18)
	Median	73.0	68.0	73.0	59.0
	Minimum, maximum	24, 100	0, 100	0, 100	0, 100
Month 6 After Optional Treatment	n	86	72	158	29
	Mean (SD)	75.1 (21.85)	69.4 (27.59)	72.5 (24.71)	63.8 (20.75)
	Median	79.0	73.0	76.0	59.0
	Minimum, maximum	0, 100	0, 100	0, 100	24, 100

Note: FACE-Q satisfaction with outcome questionnaire was not completed at the baseline visit. Only subjects who received retreatment or optional initial treatment (for no treatment subjects) had visits at Months 3 and 6 after Optional Treatment. FACE-Q satisfaction with outcome Rasch-transformed total scores range from 0 (worst) to 100 (best) (higher scores reflect a better outcome).

The secondary effectiveness endpoint proportion of participants in each response category for questions in the Subject Satisfaction Questionnaire are summarized below. Across Month 1 to Month 12, the percentages of subjects in the *Restylane Eyelight* group who responded with "very satisfied" or "satisfied" for the following questions below were higher at all visits compared with the no treatment control group.

- Made them look younger (*Restylane Eyelight*: 70.6% to 80.5%; no treatment: 0% to 2.9%)
- Made them look less tired (*Restylane Eyelight*: 78.6% to 87.3%; no treatment: 0% to 2.9%)
- Made them feel better about themselves (*Restylane Eyelight*: 74.3% to 81.9%; no treatment: 0% to 5.6%)
- Made them feel happier (*Restylane Eyelight*: 64.8% to 74.1%; no treatment: 0% to 5.6%)
- Made them feel more attractive (*Restylane Eyelight*: 70.8% to 79.2%; no treatment: 0% to 5.6%)
- Improved their self-confidence (*Restylane Eyelight*: 64.2% to 76.1%; no treatment: 0% to 5.6%)
- Improved overall satisfaction with their appearance (*Restylane Eyelight*: 76.3% to 83.4%; no treatment: 0% to 5.6%)
- Made them look the way they felt (*Restylane Eyelight*: 66.4% to 74.5%; no treatment: 0% to 2.9%)
- Reduced the shadows under their eyes (*Restylane Eyelight*: 76.3% to 83.3%; no treatment: 0% to 8.3%)
- Made them need less concealer (*Restylane Eyelight*: 58.8% to 66.4%; no treatment: 0% to 8.3%)

For the secondary effectiveness endpoint, time until the participants feel comfortable returning to social engagement after treatment, based on subject diary reporting the median time for subjects injected with needle was within 4 hours after treatment and for subjects injected with cannula within 12 hours after treatment.

The secondary effectiveness endpoint improvement rate based on the Independent Photographic Reviewer's assessment using random pairings of baseline and post-baseline

photographs showed the percentages of responders in the *Restylane Eyelight* group were higher at all visits across Month 3 to Month 12 for both sites of the face combined (65.2% to 68.6%), compared to the no treatment group (16.7% to 29.7%).

3. Subgroup Analyses

The following preoperative characteristics were evaluated for potential association with the primary effectiveness outcomes at Month 3: injection tool, study site, Fitzpatrick skin types (I-III and IV-VI), race, ethnicity, gender, BMI, age, baseline GIHS, and cannula type. The responder rates in the *Restylane Eyelight* group based on the BEs' GIHS assessments across all visits were generally similar across injection tool, race, ethnicity, and age.

In the *Restylane Eyelight* group the responder rate based on the BEs' GIHS assessments at Month 3:

- were similar in participants who received treatment via needle (89.6%) and in participants who received treatment via cannula (84.9%).
- ranged from 60.0% to 100% across study sites.
- was generally similar between participants with Fitzpatrick Skin Type (FST) I-III (87.8%) and FST IV-VI (86.6%).
- generally similar across White participants (87.3%), Black participants (86.2%), and participants of other races (94.3%).
- was generally similar between Hispanic or Latino participants (82.5%) and not Hispanic or Latino participants (88.6%).
- was generally similar between male (94.3%) and female (86.7%) participants.
- was generally similar between participants with a BMI $\leq$24.25 kg/m^2 (88.6%) and participants with a BMI >24.25 kg/m^2 (86.2%).
- was generally similar between participants $\leq$45 years of age (91.0%) and participants >45 years of age (83.8%).
- was generally similar between participants with a baseline GIHS score of moderate (88.2%) and severe (86.5%).
- was higher in participants who had a TSK 27-gauge × 1.5 inch cannula (91.2%) compared with participants who had a TSK 25-gauge × 1.5 inch cannula (69.6%).
- was generally similar between participants with onsite visits (89.2%) and participants with remote visits (91.1%).

The GIHS and GAIS endpoints were analyzed in the needle group and the cannula group separately for all visits. The responder rates based on the BEs' GIHS assessment and the subjects' and TIs' GAIS assessments were generally similar across all visits, between subjects who received *Restylane Eyelight* via needle and subjects who received *Restylane Eyelight* via cannula.

To evaluate the consistency of the AE data, subgroup analyses were performed. All AEs related to study product or injection procedure by system organ class (SOC), preferred term (PT), and maximum intensity (mild, moderate, or severe) were repeated by injection tool, study site, and FST group (I-III and IV-VI).

4. 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 16 principal investigators and 25 sub-investigators/blinded evaluator, of which none were full-time or part-time employees of the sponsor, and 6 investigators had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f). These 6 investigators had disclosable financial interests/arrangements described as significant payment of other sorts. 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.

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. 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. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

Restylane Eyelight met the primary effectiveness endpoint in the clinical study (43USTT1904). From *Restylane Eyelight* treatment, the superiority of treatment versus no treatment (responder rate difference of 69.7%; $p<0.001$) at 3 months was demonstrated. The secondary effectiveness endpoint support *Restylane Eyelight* duration for 12 months, with a statistically significantly greater responder rate versus no treatment.

Subgroup analyses were evaluated for potential association with the primary effectiveness outcomes at Month 3 for: injection tool, study site, Fitzpatrick skin types (I-III and IV-VI), race, ethnicity, gender, BMI, age, baseline GIHS, and cannula type. Treatment group participants showed consistent responder rates across different subgroups with the exception of investigational sites (range 60% to 100%) and cannula type (91.2% with TSK 27-gauge × 1.5 inch to 69.6% with TSK 25-gauge × 1.5 inch). The GIHS responder rates at 3 months were similar in participants treated using needle (89.6%) and in participants treated using cannula (84.9%).

B. Safety Conclusions

The potential risks and adverse effects of the device are based on data collected in the clinical study conducted to support the PMA supplement approval for the new indication as described above. The data submitted provide a reasonable assurance that the device is safe for deep (supraperiosteal) injection, via needle or via cannula, for improvement of infraorbital hollowing in patients over the age of 21. The specific conclusions are:

- None of the visual safety assessments (visual acuity, confrontational visual fields, and ocular motility) presented safety concerns after treatment with *Restylane Eyelight*.
- The most common pre-defined injection related events (IRE) were tenderness (89.7%), followed by swelling (85.0%). Over 77.5 % of the pre-defined IREs were tolerable and over 63.7% were limited in time with a duration of 7 days or less after initial injection, touch-up injection, and retreatment injection.
- All AEs considered related to study product or injection procedure, were mild or moderate in intensity. The most common related AEs after initial treatment were implant site swelling (3.8%), implant site pain (2.5%) and headache (2.2%), all others occurred in less than 2% of the participants.

- Eight participants had related AEs with an onset after 21 days. Two participants experienced in total 3 AEs with moderate intensity, all other were of mild intensity. For all but one subject these AEs were resolved during the study.
- No participant experienced an AE leading to study withdrawal.
- There were no participants with related SAEs in the study. One participant died due to COVID-19 during the study.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA supplement approval as described above. A complete summary of effectiveness is provided in Section X.D.2 and demonstrates the superiority of Restylane Eyelight treatment to no-treatment across a variety of analyses metrics (GIHS, GAIS, IPR, FACE-Q and subject's satisfaction questionnaire).

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA supplement approval as described above. 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 Eyelight*. Most of the participants experienced common IREs which included tenderness, swelling, pain, bruising, redness, and lumps/bumps. Participants rated the IREs as predominately tolerable and with a majority resolved within 7 days or less. Eight participants had related AEs that developed more than 21 days after treatment. All of these AEs, except for one subject (mild implant site swelling on both sites, occurring after 24 days from treatment), resolved either spontaneously or with treatment.

Major differences in outcomes are provided below.

- More AEs were reported that were related to the study product in the cannula group (4.9% in needle, 20.9% in cannula) as well as AE of special interest in the cannula group (2.5% in needle, 8.5% in cannula).

- The percentage of subjects who experienced AEs related to study product or injection procedure after initial treatment was higher for subjects who were injected at multiple depths (supraperiosteal and other) compared with subjects who were injected supraperiosteal only (29.2% and 11.3%, respectively).

- The percentage of subjects who experienced AEs related to study product or injection procedure after initial treatment was higher for subjects who received local injection of

anesthetics compared with subjects who received topical anesthetics (20.9% and 9.9%, respectively).

- There were reported differences in effectiveness (Responder rates based on the GIHS at Month 3 by cannula type) between cannula type. TSK 27-gauge × 1.5 inch cannula (91.2%) compared with subjects who had a TSK 25-gauge × 1.5 inch cannula (69.6%).

- Female subjects reported higher rates of related AEs after initial treatment including touch-up treatment than male subjects (14%, 5% respectively).

- Subjects with BMI <= 24.25 reported higher rates (18.2%) of related AEs after initial treatment including touch-up treatment than subjects with BMI > 24.25 (9.3%).

- The rates and severity of reported related AEs and IREs are generally typical and expected for dermal fillers. Higher rates of AEs were observed in female subjects, subjects with BMI less than or equal to 24.25, cannula (versus needle) and when local anesthetics were used. Patients were observed to have lower rates of AE when topical anesthetics were used compared to those who had local anesthetic. While the AE rates are higher in these groups, the overall rates of AEs were consistent with the expected AEs for dermal filler devices. Out of the 316 treated participants, 40 (12.7%) experienced an AE considered related to study product or injection procedure. Of the subjects injected via needle, 8/163 (4.9%) experienced related AEs, and 32/153 (20.9%) of the participants injected via cannula experienced related AEs. Despite these differences, given the overall low AE rate and that all AEs were mild to moderate in severity (the majority of which resolved within 7 days), the probable benefits outweigh the probable risks, as determined by the short-term IREs, the adverse events, and rare late adverse events seen after injection balanced against the improvement seen on the Galderma Infraorbital Hollow Scale and patient satisfaction.

1. <u>Patient Perspective</u>

Patient perspectives considered during the review included:

- FACE-Q Satisfaction with Outcome was assessed at 1, 3, 6, 9 and 12 months after baseline, and at 3 and 6 months after optional treatment. Results for FACE-Q are discussed in Section X.D.2, Table 16 of this document.
- GAIS assessed by the participants at 1, 3, 6, 9 and 12 months after baseline, at 1 month after optional touch-up and at 1, 3, and 6 months after optional treatment. Results for GAIS assessments are discussed in Section X.D.2, Table 14 and Table 15 of this

document.

- A subject's satisfaction questionnaire was administered to evaluate subject's satisfaction using a 5-point Likert Response Scale. Participants completed the questionnaire at 1, 3, 6, 9 and 12 months after baseline, and at 3 and 6 months after optional treatment. Results for subject's satisfaction questionnaire are discussed in Section X.D.2 of this document.
- Adverse events were obtained from sign and symptoms reported by subjects during visits. Related adverse events that were reported during the study are summarized in Section X.D.1 of this document.
- Diaries which were completed by study participants for 28 days after each treatment, were used to collect information about predefined, injection related events at the treated area. Predefined, injection related events that were reported during the study are summarized in Section X.D.1, Table 6 and Table 7 of this document. The diary was also used to record the time until the participant felt comfortable returning to social engagement after treatment, with the results presented in Section X.D.2 of this document.

In conclusion, given the available information above, the data support that for correction of infraorbital hollowing in patient 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. Based on the results of the 43USTT1904 clinical study, Restylane Eyelight demonstrated a favorable safety and effectiveness profile for injection with needle and cannula to improve infraorbital hollows in patients over the age of 21. Restylane Eyelight is shown to be statistically superior to no treatment for the indication for use. The benefits and risks of dermal fillers are sufficiently well understood for patients to make informed decisions about their use.

XIII. CDRH DECISION

CDRH issued an approval order on May 8, 2023

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

XIV. 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.