February 13, 2025

Symatese
% Karina Guillen
Vice President, Regulatory Affairs - Device
Evolus, Inc.
520 Newport Center Drive
Suite 1200
Newport Beach, California 92660

Re: P240022
Trade/Device Name: EVOLYSSE™ SMOOTH and EVOLYSSE™ FORM
Product Code: LMH
Filed: June 21, 2024
Amended: November 15, 2024

Dear Karina Guillen:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the EVOLYSSE™ SMOOTH and EVOLYSSE™ FORM. These devices are indicated for dermal and subdermal injection to correct moderate to severe dynamic facial wrinkles and folds (such as NLFs) in adults 22 years or older. We are pleased to inform you that the PMA is approved. You may begin commercial distribution of the device in accordance with the conditions of approval described below. Although this letter refers to your product as a device, please be aware that some approved products may instead be combination products. The Premarket Approval Database available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm identifies combination product submissions.

The sale and distribution of this device are restricted to prescription use in accordance with 21 CFR 801.109 and under section 515(d)(1)(B)(ii) of the Federal Food, Drug, and Cosmetic Act (the act). FDA has determined that these restrictions on sale and distribution are necessary to provide reasonable assurance of the safety and effectiveness of the device. Your device is therefore a restricted device subject to the requirements in sections 502(q) and (r) of the act, in addition to all other applicable requirements, including those governing the manufacture, distribution, and marketing of devices.

Expiration dating for this device has been established and approved at 24 months based on real time storage between 5º±3ºC and 25ºC. This is to advise you that the protocol you used to establish this expiration dating is considered an approved protocol for the purpose of extending the expiration dating as provided by 21 CFR 814.39(a)(7).

Continued approval of the PMA is contingent upon the submission of periodic reports, required under 21 CFR 814.84, at intervals of one year (unless otherwise specified) from the date of approval of the original PMA. This report, identified as "Annual Report" and bearing the applicable PMA reference number, should be submitted to the address below. The Annual Report should indicate the beginning and ending date of the period covered by the report and should include the information required by 21 CFR 814.84.

In addition to the above, and in order to provide continued reasonable assurance of the safety and effectiveness of the PMA device, under 21 CFR 814.82(a)(9), the Annual Report must include, separately for each model number (if applicable), the number of devices sold and distributed during the reporting period, including those distributed to distributors. The distribution data will serve as a denominator and provide necessary context for FDA to ascertain the frequency and prevalence of adverse events, as FDA evaluates the continued safety and effectiveness of the device.

In addition to the Annual Report requirements, you must provide the following data in post-approval study (PAS) reports for the PAS listed below.

A synopsis of the referenced PAS is presented below:

Protocol Version	Version 1.0 24-Jan-2025	**Investigational Device**	Evolysse™ Form
Study Number	TBD		
Phase	Post-Approval	**Control Device**	N/A
Indication	Dermal and subdermal injection to correct moderate to severe dynamic facial wrinkles and folds (such as nasolabial folds) in adults 22 years and older	**Study Sites**	2 US Sites
Title	Prospective, Multi-Center, Open Label Study to Evaluate the Safety and Effectiveness of Evolysse™ Form for the Treatment of Nasolabial Folds in Fitzpatrick Skin Types V and VI		
Sponsor	Symatese		
Study Duration	24 weeks	**Number of Subjects**	Up to 15 enrolled to ensure 10 treated, 20 NLFs
Study Design	This is a prospective, multi-center, open label clinical study to evaluate the safety of Evolysse Form for the treatment of nasolabial folds (NLFs) in darker Fitzpatrick skin types (FST). Up to 15 subjects with FST V or VI will be enrolled to ensure 10 subjects (4 FST V subjects and 6 FST VI subjects) are treated with Evolysse Form in both NLFs (20 NLFs total). An FST V or VI subject who seeks treatment for nasolabial folds will be eligible for the trial. At Screening (Visit 1), the Investigator will evaluate subjects' NLFs using the Wrinkle Severity Rating Scale (WSRS) and confirm eligibility (i.e., both NLFs moderate or severe on the WSRS). At Visit 1 (Week 0), eligible subjects will be enrolled, and the Investigator will inject the study device as per the product labeling. The Investigator (or designee) will call subjects at 72 hours post-treatment. Subjects will attend in-clinic visits at Visit 2 (Week 2). At Visit 2 (Week 2) the Investigator will assess the subject for optimal aesthetic outcome and administer a touch-up if required. The Investigator (or designee) will call subjects 72 hours post touch-up. Subjects will attend in-clinic visits at Visit 3 (Week 4) and Visit 4 (Week 24). Visit 4 (Week 24) will be the Exit visit. Subjects will report their Injection Site Responses (ISRs) in a subject diary for up to 28 days after each injection.		
Primary Objective	Evaluate the safety and effectiveness of Evolysse Form in subjects with Fitzpatrick skin types V and VI.		
Inclusion Criteria	1. Subject is aged 22 or older. 2. Subject with Fitzpatrick skin type V or VI who has bilateral moderate to severe nasolabial folds on the WSRS as assessed by the Investigator. 3. Subject willing to abstain from other facial aesthetic procedures in or adjacent to the NLFs (such as the cheek) through the last study follow-up visit that could interfere with treatment outcomes (e.g., facial fillers, skin laser and radiofrequency therapy such as Thermage, chemical re-surfacing, dermabrasion, Botulinum toxin injections, aesthetic facial surgery, other facial treatments of the NLFs or adjacent areas). 4. Subject understands and accepts the obligation to present for all scheduled follow-up visits and is logistically able to meet all study requirements. 5. Subject with facial hair which may obstruct the assessment of the treatment area, must be agreeable with non-laser removal of facial hair prior to assessment visits. 6. Subject willing to provide written informed consent for their participation in the study.		

Exclusion Criteria	1. Subject is a female of childbearing potential (e.g., not postmenopausal for at least one year or has not had a hysterectomy or tubal ligation) not using medically effective birth control (e.g., hormonal methods in use at least 30 days prior to injection or barrier methods such as condom and spermicide in use at least 14 days prior to injection) or is pregnant, lactating, or plans to become pregnant during the study. 2. Subject has participated in a clinical study in which an investigational device or drug was received in the 30 days prior to screening or plans to enroll in such a study during the course of the current study. 3. Subject is an employee or direct relative of an employee of the investigational site or study sponsor. 4. Subject who has received surgery in the NLFs. 5. Subject has a serious or progressive disease, which, in the investigator's judgment, puts the subject at undue risk (e.g., uncontrolled diabetes, autoimmune disease, cardiac pathologies). 6. Subject has an acute inflammatory process or infection, or history of chronic or recurrent infection or inflammation with the potential to interfere with the study results or increase the risk of adverse events. 7. Subject has a disorder that may impact wound healing such as connective tissue or immunosuppressive disorder. 8. Subject has a current local lesion or a recent history of precancerous lesions/skin malignancies in the local treatment area that in the opinion of the Investigator may impact treatment or evaluations. 9. Subject has had an active skin disease in the NLF area. 10. Subject has scars, infection, rosacea, herpes, acne, blotches or other pathology in the NLFs. 11. Subject has a past history of allergy or hypersensitivity to gram positive bacterial proteins. 12. Subject is predisposed to keloidosis or hypertrophic scarring. 13. Subject has a known history of hyper- or hypo-pigmentation in the NLFs. 14. Subject with known allergy to hyaluronic acid, lidocaine, or amide type anesthetics. 15. Subject has a known history of multiple allergies, allergic/anaphylactic reactions. 16. Subject has a known bleeding disorder. 17. Subject has received any medication which, in the judgement of the investigator, may interfere with the study objectives. 18. Subject has received within the past week or plans to receive up to 1 week after treatment high-dose Vitamin E, aspirin, anti-inflammatories, antiplatelets, or thrombolytics. 19. Subject has received within the past 12 months or plans to receive during the study any injections outside of those in the study protocol including non-permanent fillers (e.g., hyaluronic acid, CaHA) on the face. 20. Subject has received within the past 12 months or plans to receive during the study neurotoxin injections below the orbital rim (forehead and glabella are acceptable). 21. Subject has received at any time or plans to receive during the study a permanent filler (e.g., polylactic acid, PMMA, silicone) on the face. 22. Subject has received within the past 6 months or plans to receive during the study ablative or non-ablative dermal resurfacing procedures. 23. Subject has received in the past 3 months or plans to receive during the study non-invasive skin tightening procedures on the face. 24. Subject has received in the past 2 weeks or plans to receive during the study prescription facial wrinkle therapies (RENOVA), topical steroids, skin irritating topical preparations, or self-tanning agents on the face.

Prohibited Therapies and Procedures	Facial or cosmetic procedures have either usage restrictions, or are prohibited during the study and appropriate washout periods must be respected: • **Dermal fillers used in the face (below the orbital rim), and above the neck:** Bioresorbable fillers (≤12 months), permanent implants, permanent fillers, semi-permanent fillers (any previous use prohibited); • **Systemic medications:** NSAIDS, fish oil, high dose oral vitamin E, ASA (≤7 days pre-Tx, ≤7 days post-Tx), corticosteroids or interferon (≤7 days pre-Tx, ≤30 days post-Tx), anti-coagulation therapy or vaccine of any type (≤14 days pre-Tx, ≤14 days post-Tx); • **Procedures/treatments in the face (below the orbital rim), and above the neck:** - Laser/light therapies, chemical peel (light), dermabrasion, Rx strength topical retinoids (≤3 months); - Deep chemical peel, non-invasive skin-tightening, mesotherapy, fat injections, botulinum toxin injection (*frontalis and glabella treatment permitted)*, excisional facial surgery (≤6 months); - Clinically significant oral or maxillofacial surgery (≤12 months); - Elective dental surgeries (≤14 days pre-Tx, ≤14 days post-Tx) - Lifting threads (any previous use prohibited); • **Investigational drugs/devices:** Exposure to non-study investigational drug/device (≤30 days).
Device Administration	Subjects will receive initial injections of the study device in both NLFs at Visit 1 to optimal correction (over-correction is prohibited). At Week 2 (Visit 2), additional correction with the study device will be provided if deemed necessary by the Investigator. The maximum volume per administration session is 2.0 mL per NLF at each injection session without overcorrection. Study devices will be injected into the dermis and/or subdermis at the discretion of the Investigator. Study devices will be injected using the standard needles accompanying the study device, and may be administrated using linear threading, serial puncture injections, cross-hatching or a combination thereof. The study device contains lidocaine, and additional anesthesia is prohibited (e.g., EMLA, dental blocks, ice, etc.). Ice and/or acetaminophen may be used at the discretion of the Investigator for post-injection treatment for pain or discomfort.
Safety Evaluations	1. AEs across the duration of the study (incidence and severity). 2. AEs of Special Interest (AESI) across the duration of the study (i.e., visual disturbances such as loss of vision, blurriness, double vision, pain in or around the eyes, blindness, blind spot or shadow in the visual field, trouble moving eyes, ocular hypotonia, ptosis, etc.). 3. Post-injection Injection Site Responses (28-Day ISR; incidence, severity, and duration). 4. Visual assessments (Snellen visual acuity, confrontational visual field test, ocular motility). 5. Injection Site (100 mm VAS) pain immediately after treatment, and at 5, 15, and 30 minutes post-treatment.
Effectiveness Evaluations	1. Wrinkle Severity Rating Scale (WSRS): Validated 5-point scale assessing wrinkle severity. 2. Global Aesthetic Improvement Scale (GAIS): Subjective 5-point dynamic scale. 3. FACE-Q Appraisal of Nasolabial Folds: Validated Patient Reported Outcome Measure assessing subjects' nasolabial folds. 4. FACE-Q Satisfaction with Outcome: Validated Patient Reported Outcome Measure assessing subjects' satisfaction with the result of the procedure.

Primary Effectiveness Endpoint	The primary effectiveness endpoint uses the Week 24 and baseline WSRS scores as determined by a photographic review panel. The WSRS data from this study will be compared with the historical control (Restylane-L) data from the pivotal study for statistical non-inferiority. A non-inferiority margin of 0.5 grade difference in WSRS mean change from baseline between the NLFs treated with Evolysse Form from this study and the NLFs treated with Restylane-L from the pivotal study will be used to test the primary hypothesis.
Secondary Effectiveness Endpoints	Secondary effectiveness endpoints will be evaluated using descriptive statistics. 1. WSRS (Investigator) mean change from baseline at Week 24 based on live assessments 2. WSRS (Investigator) responder rate by NLF at Week 24 (NLF deemed responder if ≥ 1-grade improvement) based on live assessments 3. WSRS (Investigator) responder rate by subject at Week 24 (subject deemed responder if both NLFs show ≥ 1-grade improvement) based on live assessments 4. GAIS (Subject) responder rate at Week 24 5. FACE-Q Appraisal of Nasolabial Folds mean change from baseline at Week 24 6. FACE-Q Satisfaction with Outcome at Week 24
Statistical Methods	**Analysis Population:** The Safety Population is defined as subjects who received study treatment. **Descriptive Methods:** For categorical parameters, the number and percentage of subjects/observations in each category will be presented. The denominator will be based on the number of subjects/observations appropriate for the purpose of analysis. For continuous parameters, descriptive statistics will include n (number of subjects or observations), mean, standard deviation, median, and range. **Primary Endpoint:** The primary endpoint will compare WSRS data between this study and the historical control (Restylane-L) from the pivotal study. The WSRS mean change from baseline at Week 24 for the NLFs treated with Evolysse Form in this study will be determined based on photographic review panel assessment and compared with the historical photographic review panel data on the Restylane-L treated NLFs from the pivotal study. The WSRS data will be analyzed in a non-inferiority statistical model with a non-inferiority margin of 0.5 grade for the difference in WSRS mean change from baseline between NLFs treated with Evolysse Form in this study and NLFs treated with Restylane-L from the pivotal study. Expressing the difference between treatment groups as the WSRS mean change from baseline in the Evolysse Form group minus the WSRS mean change from baseline in the Restylane-L group, the lower bound of the two-sided 95% CI must be > -0.5 grades in order to demonstrate Evolysse Form non-inferiority. The CI will be based on a t-test of mean change from baseline. Mean change from baseline is expected to be normally distributed; however, if the normality assumption for the t-test is not met based on the Shapiro-Wilk test, the confidence intervals will be estimated by the Bootstrap method to assess non-inferiority. **Secondary Endpoints** will be evaluated with descriptive statistics and using the Safety Population. **Safety Evaluations:** Safety evaluations will be summarized using the Safety Population. Point estimates for all ISRs and AEs will be presented, and Wilson 95% confidence intervals will be calculated for the overall incidence of AEs and SAEs.
Sample Size	Up to 15 subjects with FST V or VI will be enrolled to ensure 10 subjects (4 FST V and 6 FST VI) are treated with Evolysse Form in both NLFs (20 NLFs total).

TABLE 1. STUDY SUMMARY TABLE

	BL			If T/U at V2		
Visit Week	V1 W0	V1 Phone f/u 72hrs	V2 W2	V2 Phone f/u 72hrs	V3 W4	V4 W24
Written informed consent	X					
Demographics, Hx (med/surg/ophthal)	X					
Inclusion/exclusion criteria	X					
UPT	X					
Concomitant Medications	X	X	X	X	X	X
Photography [1]	X		X		X	X
Study device injections	X		X[2]			
ISR diary • dispense (D) • review (R)	D		D[3] R		R	
TI Assessments						
Visual assessments[4]	X		X		X	X
Adverse Events	X	X	X	X	X	X
Subject Assessments						
Pain VAS	X					
WSRS	X					X
GAIS						X
FACE-Q Appraisal of Nasolabial Folds	X					X
FACE-Q Satisfaction with Outcome						X

BLE = Blinded Live Evaluator; LFS = Lip Fullness Scale; GAIS = Global Aesthetic Improvement Scale; IPR = Independent Panel Review; ISR = Injection Site Response; TI = Treating Investigator; T/U = Touch-up; UPT = urine pregnancy test; V = visit; VAS = visual analogue scale; W = week; d = day.

1. Photography performed pre- and post-injection (when applicable).
2. Study device injections administered if touch-up treatment required as determined by the TI.
3. ISR diary dispensed if touch-up treatment administered.
4. Snellen visual acuity, confrontational visual field test, ocular motility test; in the event of visual disturbances, a basic neurological examination must be performed.

From the time of study protocol approval, you must meet the following timelines for the above PAS:

- First subject enrolled within 6 months
- 20% of subjects enrolled within 12 months
- 50% of subjects enrolled within 18 months
- 100% of subjects enrolled within 24 months

In addition, you must submit separate periodic reports on the progress of the PAS as follows:

- Within 90 days of receipt of the approval letter, you will submit a PMA supplement that includes a complete protocol for the PAS;
- PAS progress reports will be submitted every 6 months following receipt of the approval letter;
- A Final PAS Report will be submitted within 3 months following completion of the PAS study.

For all other condition of approval studies, you must submit separate PAS Progress Reports for each study, every six (6) months for the first two (years) and annually thereafter, unless otherwise specified by FDA.

Each PAS report should be submitted to the address below identified as a "PMA Post-Approval Study Report" in accordance with how the study is identified above and bearing the applicable PMA reference number.

Be advised that failure to comply with any post-approval requirement, including at least 4 FST V and at least 6 FST VI subjects completing the study, constitutes grounds for FDA withdrawal of approval of the PMA in accordance with 21 CFR 814.82(c) and 814.46(a)(2).

Be advised that the failure to conduct any such study in compliance with the good clinical laboratory practices in 21 CFR part 58 (if a non-clinical study subject to part 58) or the institutional review board regulations in 21 CFR part 56 and the informed consent regulations in 21 CFR part 50 (if a clinical study involving human subjects) may be grounds for FDA withdrawal of approval of the PMA in accordance with 21 CFR 814.46(a)(3)-(4).

Be advised that protocol information, interim and final results will be published on the Post Approval Studies Program Database Webpage, available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma_pas.cfm.

In addition, the results from any post approval study should be included in the labeling as these data become available. Under 21 CFR 814.39, any updated labeling must be submitted to FDA in the form of a PMA Supplement. For more information on post-approval studies, see the FDA guidance document entitled, "Procedures for Handling Post-Approval Studies Imposed by by Premarket Approval Application Order " (https://www.fda.gov/media/71327/download).

This is a reminder that as of September 24, 2014, class III devices are subject to certain provisions of the final Unique Device Identification (UDI) rule. These provisions include the requirement to provide a UDI on the device label and packages (21 CFR 801.20), format dates on the device label in accordance with 21 CFR 801.18, and submit data to the Global Unique Device Identification Database (GUDID) (21 CFR 830 Subpart E). Additionally, 21 CFR 814.84 (b)(4) requires PMA annual reports submitted after September 24, 2014, to identify each device identifier currently in use for the subject device, and the device identifiers for devices that have been discontinued since the previous periodic report. It is not necessary to identify any device identifier discontinued prior to December 23, 2013. Combination Products may also be subject to UDI requirements (see 21 CFR 801.30). For more information on these requirements, please see the UDI website, https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/unique-device-identification-udi-system.

Before making any change affecting the safety or effectiveness of the PMA device, you must submit a PMA supplement or an alternate submission (30-day notice) in accordance with 21 CFR 814.39. All PMA supplements and alternate submissions (30-day notice) must comply with the applicable requirements in 21 CFR 814.39. Additional information about changes that may require a PMA supplement are provided in the FDA guidance document entitled, "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process" https://www.fda.gov/media/81431/download.

You are reminded that many FDA requirements govern the manufacture, distribution, and marketing of devices. For example, in accordance with the Medical Device Reporting (MDR) regulation, 21 CFR 803.50 and 21 CFR 803.52 for devices or post-marketing safety reporting (21 CFR 4 Part 4, Subpart B) for combination products, you are required to report adverse events for this device. Manufacturers of medical devices, including in vitro diagnostic devices, are required to report to FDA no later than 30 calendar days after the day they receive or otherwise becomes aware of information, from any source, that reasonably suggests that one of their marketed devices:

1. May have caused or contributed to a death or serious injury; or

2. Has malfunctioned and such device or similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Additional information on MDR, including how, when, and where to report, is available at https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems and on combination product post-marketing safety reporting is available at (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products).

In accordance with the recall requirements specified in 21 CFR 806.10 for devices or the post-marketing safety reporting requirements (21 CFR 4 Part 4, Subpart B) for combination products, you are required to submit a written report to FDA of any correction or removal of this device initiated by you to: (1) reduce a risk to health posed by the device; or (2) remedy a violation of the act caused by the device which may present a risk to health, with certain exceptions specified in 21 CFR 806.10(a)(2). Additional information on recalls is available at https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/industry-guidance-recalls.

CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading. CDRH will notify the public of its decision to approve your PMA by making available, among other information, a summary of the safety and effectiveness data upon which the approval is based. The information can be found at https://www.fda.gov/medical-devices/device-approvals-denials-and-clearances/pma-approvals. Written requests for this information can also be made to the Food and Drug Administration, Dockets Management Branch, (HFA-305), 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by submitting a petition for review under section 515(g) of the act and requesting either a hearing or review by an independent advisory committee. FDA may, for good cause, extend this 30-day filing period.

Failure to comply with any post-approval requirement constitutes a ground for withdrawal of approval of a PMA. The introduction or delivery for introduction into interstate commerce of a device that is not in compliance with its conditions of approval is a violation of law.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with a copy of all final labeling. Final labeling that is identical to the labeling approved in draft form will not routinely be reviewed by FDA staff when accompanied by a cover letter stating that the final labeling is identical to the labeling approved in draft form. If the final labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

All required documents should be submitted, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center - WO66-G609

10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

If you have any questions concerning this approval order, please contact John Azeke at 301-796-8042 or John.Azeke@fda.hhs.gov.

Sincerely,

BLETA VUNIQI -S Digitally signed by BLETA VUNIQI -S
Date: 2025.02.13 13:43:16 -05'00'

Bleta Vuniqi
Deputy Office Director
OHT4: Office of Surgical and Infection Control Devices
Office of Product Evaluation and Quality
Center for Devices and Radiological Health