SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Injectable Dermal Filler

Device Trade Name: EVOLYSSE™ SMOOTH
EVOLYSSE™ FORM

Device Pro code: LMH (Implant, Dermal, For Aesthetic Use)

Applicant's Name and Address: Symatese
520 Newport Center, Suite 1200
Newport Beach, CA
92660

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P240022

Date of FDA Notice of Approval: February 13, 2025

II. INDICATIONS FOR USE

EVOLYSSE™ SMOOTH is indicated for dermal and subdermal injection to correct moderate to severe dynamic facial wrinkles and folds (such as nasolabial folds) in adults 22 years or older.

EVOLYSSE™ FORM is indicated for dermal and subdermal injection to correct moderate to severe dynamic facial wrinkles and folds (such as nasolabial folds) in adults 22 years or older.

III. CONTRAINDICATIONS

- EVOLYSSE™ SMOOTH and EVOLYSSE™ FORM are contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.
- EVOLYSSE™ SMOOTH and EVOLYSSE™ FORM may contain trace amounts of Gram-positive bacterial proteins and are contraindicated for patients with a history of allergies to such material.
- EVOLYSSE™ SMOOTH and EVOLYSSE™ FORM contain lidocaine and are contraindicated for patients with a history of allergies to such material.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the EVOLYSSE™ SMOOTH and EVOLYSSE™ FORM labeling.

V. DEVICE DESCRIPTION

EVOLYSSE™ SMOOTH and EVOLYSSE™ FORM are a sterile, bioabsorbable, colorless gel implants containing hyaluronic acid (HA) with 3 mg/mL lidocaine hydrochloride (HCl) in physiologic buffer. EVOLYSSE™ SMOOTH contains 20 mg/mL HA and EVOLYSSE™ FORM contains 22 mg/mL HA. The HA is produced by Streptococcus species of bacteria and is crosslinked with 1,4-butanediol diglycidyl ether (BDDE). The local anesthetic lidocaine is included to reduce pain and improve comfort during and post-injection.

The gels are supplied sterile in 1 mL plastic syringes assembled with plunger rods and finger rests. EVOLYSSE™ SMOOTH is provided with two 30G ½" sterile needles for injection. EVOLYSSE™ FORM is provided with one 30G ½" sterile needle and one 27G ½" sterile needle for injection. EVOLYSSE™ SMOOTH, EVOLYSSE™ FORM, and the needles are for single use only.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several alternatives for the correction of dynamic facial wrinkles and folds including various minimally invasive injectable procedures (e.g., other FDA-approved soft tissue fillers and autologous fat transfer) and surgery (e.g., rhytidectomy). Each alternative has its own advantages and disadvantages. Patients should fully discuss these alternatives with their physician to select the method that best meets their expectations and lifestyle.

VII. MARKETING HISTORY

EVOLYSSE™ FORM first received the CE Mark under the EU Medical Device Directive as ESTYME™ LIFT in January 2021 and has also been approved in Brazil since August 2022. Both EVOLYSSE™ SMOOTH and EVOLYSSE™ FORM received the CE Mark under the EU Medical Device Regulation as ESTYME™ SMOOTH and ESTYME™ FORM in November 2024.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device. These adverse effects which are common for soft tissue filler treatments include tenderness, swelling, lumps, bruising, redness, pain, discoloration, and itching. Rare, but serious adverse events associated with the intravascular injection of soft tissue fillers in the face have been reported and include temporary or permanent vision impairment, blindness, cerebral ischemia or cerebral hemorrhage leading to stroke, skin necrosis, and damage to underlying facial structures.

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

EVOLYSSE™ SMOOTH and EVOLYSSE™ FORM were characterized through physical and chemical testing (Table 1).

Table 1: Physical and Chemical Testing for EVOLYSSE™ SMOOTH and EVOLYSSE™ FORM

Test	Purpose	Results
Gel Appearance	Ensures gel appearance meets specifications	Passed
Total HA Content	Ensures total HA content meets specifications	Passed
Lidocaine HCl Content	Ensures lidocaine HCl content meets specifications	Passed
Extrusion Force	Ensures extrusion force meets specifications	Passed
Rheology	Ensures rheology meets specifications	Passed
pH	Ensures pH meets specifications	Passed
Osmolality	Ensures osmolality meets specifications	Passed
Residual Crosslinker	Ensures residual crosslinker meets specifications	Passed
Bacterial Endotoxin	Ensures bacterial endotoxins meets specifications	Passed
Sterility	Ensures sterility of the products	Passed

Stability data for EVOLYSSE™ SMOOTH and EVOLYSSE™ FORM were collected for 36 months under ICH Q1A(R) storage conditions at 25ºC ± 2ºC / 60% ± 5% relative humidity (RH). At each timepoint, the products were evaluated for conformance with microbiological, and physical and chemical properties including lidocaine HCl potency and lidocaine-related degradants. Conformance with all specifications was confirmed.

B. Biocompatibility Studies

EVOLYSSE™ SMOOTH and EVOLYSSE™ FORM were evaluated via *in vitro* and *in vivo* biocompatibility studies per ISO 10993 (Table 2).

Table 2: Biocompatibility Testing for EVOLYSSE™ SMOOTH and EVOLYSSE™ FORM

Test	Method	Standard	Result
Cytotoxicity	MTS Assay	ISO 10993-5	Non-cytotoxic
Sensitization	Guinea Pig Maximization Test	ISO 10993-10	Non-sensitizing
Intracutaneous Reactivity	72-Hour and 14-Day Exposure in Rabbits	ISO 10993-10	Similar level of reactivity as control[a] Non-irritant at 14 days

Test	Method	Standard	Result
Acute Systemic Toxicity	Intraperitoneal Injections in Mice	ISO 10993-11	Non-toxic
Systemic Toxicity (13 Weeks)	Subcutaneous Injections in Rats	ISO 10993-11	Non-toxic
Subcutaneous Implantation[b]	Subcutaneous Injections in Rats	ISO 10993-6	Minimal to no local tissue reaction
Genotoxicity	Bacterial Reverse Mutation Micronucleus Mouse Lymphoma Assay	ISO 10993-3	Non-mutagenic Non-genotoxic
Pyrogenicity	Rabbit Pyrogen Study	USP <151>	Non-pyrogenic

[a] The control was a soft tissue filler that is FDA-approved for a similar indication.
[b] Implantation study for EVOLYSSE™ SMOOTH was 13 weeks. Implantation studies for EVOLYSSE™ FORM were 13 and 36 weeks.

Carcinogenicity Risks: The excess cancer risks for EVOLYSSE™ SMOOTH and EVOLYSSE™ FORM are in the same range of acceptable cancer risks as other previously approved soft tissue filler products.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness for dermal and subdermal injections with EVOLYSSE™ SMOOTH and EVOLYSSE™ FORM to correct moderate to severe dynamic facial wrinkles and folds (such as nasolabial folds) in the US under IDE G210231. Data from this clinical study was the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Subjects were treated between May 17, 2022, and March 5, 2024. The database for this PMA reflected data collected through May 15, 2024, and included 140 subjects who were randomized and treated. There were 6 investigational sites.

EVOLYSSE™ SMOOTH and EVOLYSSE™ FORM was evaluated in a prospective, randomized, split-face, double blind, controlled clinical study for the correction of NLFs. To be eligible for the study, subjects were required to have a score of 3 (moderate) or 4 (severe) in both NLFs on the Wrinkle Severity Rating Scale (WSRS).

Subjects were randomized to receive initial treatment with EVOLYSSE™ SMOOTH or EVOLYSSE™ FORM in one NLF and the control (Restylane-L) in the contralateral NLF. At 2 weeks, subjects were assessed for an optional touch-up treatment using the same products as the initial treatment. Subjects were followed for 12 months after the initial treatment, at which point they were offered an optional retreatment with either EVOLYSSE™ SMOOTH or EVOLYSSE™ FORM (depending on the product injected at initial treatment) in both NLFs and an optional touch-up treatment 2 weeks later. Retreatment subjects were followed for 3 months after the initial retreatment.

The primary effectiveness endpoint was defined using the baseline and 6-month scores on the validated 5-point WSRS as determined from an independent photographic review (IPR) by three trained raters. For each subject, the change from baseline to month 6 was determined for the treatment (EVOLYSSE™ SMOOTH or EVOLYSSE™ FORM) and control NLFs, which were then used to calculate the difference in change between NLFs. The primary endpoint was met if the mean of the differences at 6 months (control NLF change minus treatment NLF change) was less than a 0.5 grade change to demonstrate non-inferiority.

The control group was the contralateral NLF treated with a legally marketed alternative approved for a similar indication for use.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the CLIN2101 study was limited to subjects who met the following key inclusion criteria:

   - Subject was aged 22 and older.
   - Subject had bilateral moderate to severe nasolabial folds on the WSRS as scored by a live, masked evaluator.

   Patients were not permitted to enroll in the CLIN2101 study if they met any of the following exclusion criteria:

   - Subject was a female of childbearing potential (e.g., not postmenopausal for at least one year or had 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 was pregnant, lactating, or planned to become pregnant during the study.
   - Subject received surgery in the NLFs, or had plans to during the study.
   - Subject had a serious or progressive disease, which, in the investigator's judgment, put the subject at undue risk (e.g., diabetes, autoimmune pathology, cardiac pathologies).
   - Subject had 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.
   - Subject had a disorder that may impact wound healing such as connective tissue or immunosuppressive disorder.
   - Subject had 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.
   - Subject had an active skin disease in the NLF area.

- Subject had scars, infection, rosacea, herpes, acne, blotches or other pathology in the NLFs.
- Subject had a past history of allergy or hypersensitivity to gram positive bacterial proteins.
- Subject was predisposed to keloidosis or hypertrophic scarring.
- Subject had a known history of hyper- or hypo-pigmentation in the NLFs.
- Subject with known allergy to hyaluronic acid, lidocaine, or amide local anesthetics.
- Subject had a known history of multiple allergies, allergic/anaphylactic reactions.
- Subject had a known bleeding disorder.
- Subject had received any medication which, in the judgement of the investigator, may interfere with the study objectives.
- Subject had received within the past week or planned to receive up to 1 week after treatment high-dose Vitamin E, aspirin, anti-inflammatories, antiplatelets, or thrombolytics.
- Subject had received within the past 12 months or planned 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.
- Subject had received within the past 12 months or planned to receive during the study neurotoxin injections below the orbital rim (forehead and glabella are acceptable).
- Subject had received at any time or planned to receive during the study a permanent filler (e.g., polylactic acid, PMMA, silicone) on the face.
- Subject has received within the past 6 months or planned to receive during the study ablative or non-ablative dermal resurfacing procedures.
- Subject had received in the past 3 months or planned to receive during the study non-invasive skin tightening procedures on the face.
- Subject had received in the past 2 weeks or planned to receive during the study prescription facial wrinkle therapies (RENOVA), topical steroids, skin irritating topical preparations, or self-tanning agents on the face.
- Subject had a known history of rapid weight loss/gain or planned to begin a weight loss program during the study (5% of body weight).

2. Follow-up Schedule

   All subjects were scheduled to return for follow-up examinations at 6 weeks, and 3, 6, 9, and 12 months after the initial treatment.

Prior to treatment, subjects were assessed for nasolabial fold severity using the WSRS. Qualified subjects were randomized and treated with EVOLYSSE™ SMOOTH™ or EVOLYSSE™ FORM in one NLF and the control in the contralateral NLF. Optional touch-up treatments were administered two weeks after the initial treatment. Subjects were followed for 12 months after the initial treatment. At follow-up visits, nasolabial folds severity was scored using the WSRS, aesthetic improvement was assessed using the Global Aesthetic Improvement Scale (GAIS), and subject satisfaction was evaluated using the FACE-Q Appraisal of Nasolabial Folds questionnaire.

At 12 months, subjects were offered an optional retreatment with either EVOLYSSE™ SMOOTH™ or EVOLYSSE™ FORM (depending on the product injected at initial treatment) in both NLFs and an optional touch-up treatment 2 weeks later. Retreatment subjects were followed for 3 months after the initial retreatment. 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, subjects used preprinted diary forms to record specific signs and symptoms of common treatment responses (CTRs) experienced during the 30 days after initial treatment and retreatment (if performed). Adverse events (AEs) were reported by treating investigators over the course of the study and included CTRs that were ongoing at the end of the subject diaries.

The primary effectiveness endpoints were non-inferiority analyses of EVOLYSSE™ SMOOTH and EVOLYSSE™ FORM versus control at 6 months based on the validated 5-point Wrinkle Severity Rating Scale (WSRS) scores assigned to photos by an independent photo review (IPR) panel. The primary endpoint used the WSRS in the way in which it was validated (i.e., photo assessments). The WSRS descriptors are shown in Table 3.

Secondary effectiveness endpoints included:

- WSRS responder rates (defined as the percentage of subjects with at least a 1-point improvement since baseline) based on the IPR and blinded live evaluator (BLE) assessments
- GAIS responder rates (defined as subjects rated as improved, much improved, or very much improved compared to baseline) based on BLE and subject assessments
- Subject satisfaction based on the validated FACE-Q Appraisal of Nasolabial folds questionnaire

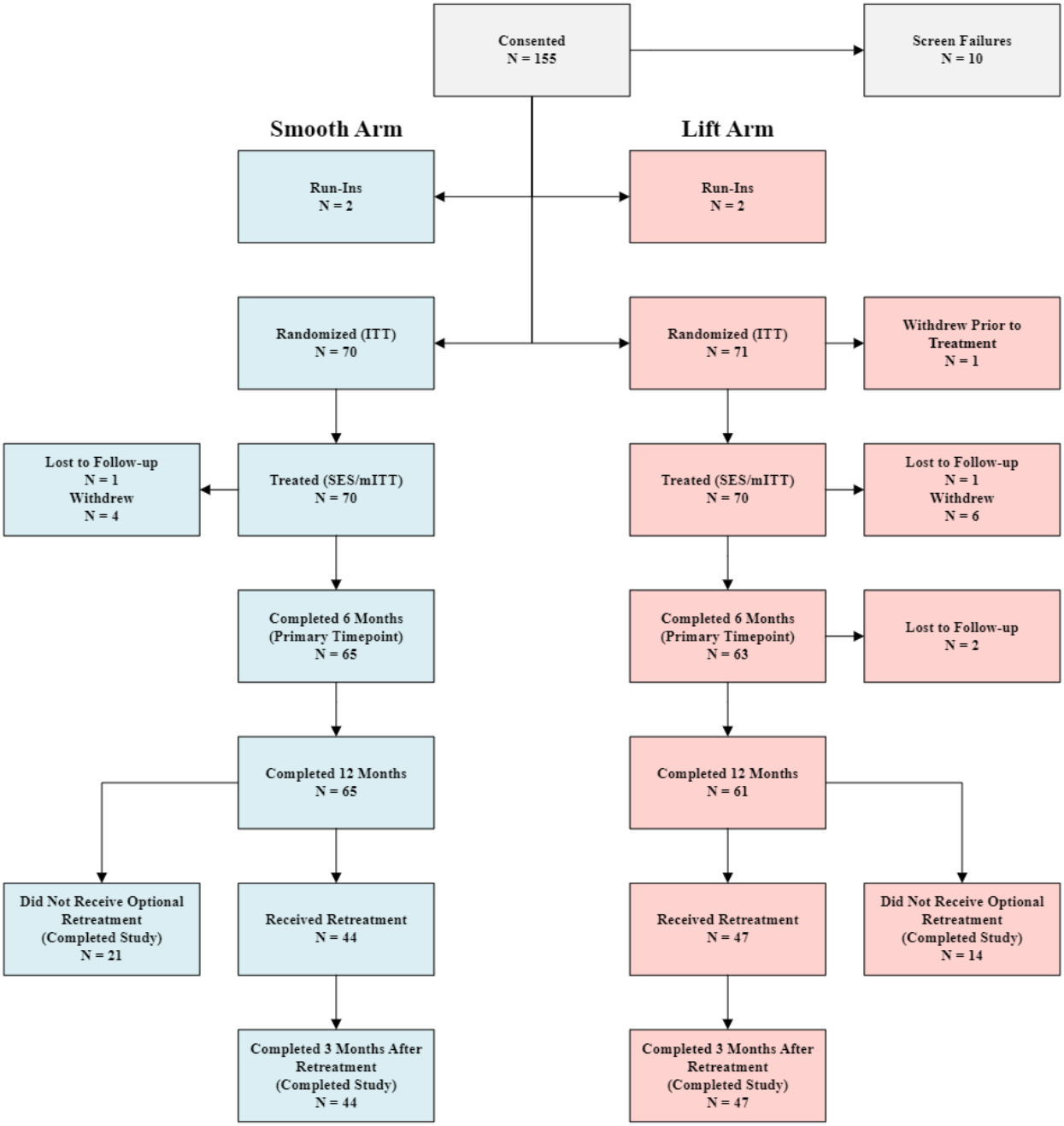
Table 3: Wrinkle Severity Rating Scale (WSRS)

Grade	Name	Description
1	Absent	No visible NLF Continuous skin line
2	Mild	Shallow but visible NLF with a slight indention
3	Moderate	Moderate deep NLF visible at normal appearance
4	Severe	Very long and deep NLF Prominent facial feature <2 mm visible fold if stretched
5	Extreme	Extremely deep, long NLF 2-4 mm V shaped fold if stretched

B. Accountability of PMA Cohort

At the time of the database lock, of the 70 subjects each randomized and treated in the two treatment arms, 65 (92.9%) subjects in the EVOLYSSE™ SMOOTH arm and 61 (87.1%) subjects in the EVOLYSSE™ FORM arm were available for analysis at study completion (i.e., 12 months after initial treatment or 3 months after the optional retreatment offered at 12 months). Subject disposition for the CLIN2101 study is shown in Figure 1.

Figure 1: Subject Disposition



C. Study Population Demographics and Baseline Characteristics

The demographics of the study population are typical for a soft tissue filler pivotal study performed in the US. The study population demographics and baseline characteristics are presented in Table 4. The distribution for sex, age, race, ethnicity, and Fitzpatrick skin type of the subjects enrolled in the study is consistent with the US population who seek treatment with soft tissue fillers for the correction of moderate to severe dynamic facial wrinkles and folds.

Table 4: Study Population Demographics and Baseline Characteristics

Demographic/Characteristic	EVOLYSSE™ SMOOTH Arm (N = 70)	EVOLYSSE™ FORM Arm (N = 70)
Age		
Mean	57.3	58.8
Min, Max	31 – 84	25-83
Sex		
Female	57 (92.9%)	66 (94.3%)
Male	5 (7.1%)	4 (5.7%)
Race		
White	50 (71.4%)	51 (72.9%)
Black/African American	19 (27.1%)	14 (20.0%)
Other	0	2 (2.9%)
Asian	0	2 (2.9%)
Multiple	1 (1.4%)	1 (1.4%)
Ethnicity		
Hispanic or Latino	18 (25.7%)	21 (30.0%)
Not Hispanic or Latino	52 (74.3%)	49 (70.0%)
Fitzpatrick Skin Type		
I	1 (1.4%)	2 (2.9%)
II	16 (22.9%)	19 (27.1%)
III	22 (31.4%)	22 (31.4%)
IV	14 (20.0%)	16 (22.9%)
V	11 (15.7%)	9 (12.9%)
VI	6 (8.6%)	2 (2.9%)
Median Baseline WSRS Score		
EVOLYSSE™ NLF	3	3
Control NLF	3	3

D. Safety and Effectiveness Results

1. Safety Results

   The analysis of safety was based on the randomized and treated population which included 70 subjects in the EVOLYSSE™ SMOOTH arm and 70 subjects in the EVOLYSSE™ FORM arm.

   Subjects used preprinted diary forms to record specific signs and symptoms of

CTRs experienced during the 30 days after initial treatment and retreatment (if performed). Subjects were instructed to rate each CTR listed on the diary as Mild, Moderate, Severe, or None.

- None or not applicable.
- Mild CTRs were defined as signs and symptoms that can be easily tolerated, can be ignored and disappear when distracted.
- Moderate CTRs were defined as signs and symptoms that cause discomfort and interfere with normal functioning but are tolerable, and cannot be ignored and do not disappear when distracted.
- Severe CTRs were defined as signs and symptoms that affect usual daily activity and incapacitate, thereby interrupting daily activities.

The severity and duration of CTRs reported by >5% of subjects after initial treatment with EVOLYSSE™ SMOOTH are summarized in Table 5 and Table 6, respectively. The incidence and severity of CTRs were similar between the EVOLYSSE™ SMOOTH and control NLFs with most CTRs reported as mild or moderate and resolving within 7 days. The incidence of CTRs was lower after retreatment with EVOLYSSE™ SMOOTH.

Table 5: Common Treatment Responses by Maximum Severity After Initial Treatment with EVOLYSSE™ SMOOTH and Control Occurring in > 5% of Treated Subjects (N = 64)

CTR	EVOLYSSE™ SMOOTH				Control			
	Total % (n)	Mild % (n)	Moderate % (n)	Severe % (n)	Total % (n)	Mild % (n)	Moderate % (n)	Severe % (n)
Tenderness	64.1% (41)	48.4% (31)	12.5% (8)	3.1% (2)	65.6% (42)	43.8% (28)	17.2% (11)	4.7% (3)
Swelling	56.3% (36)	32.8% (21)	23.4% (15)	0	62.5% (40)	37.5% (24)	21.9% (14)	3.1% (2)
Lumps	53.1% (34)	32.8% (21)	17.2% (11)	3.1% (2)	59.4% (38)	32.8% (21)	23.4% (15)	3.1% (2)
Bruising	51.6% (33)	28.1% (18)	20.3% (13)	3.1% (2)	54.7% (35)	31.3% (20)	14.1% (9)	9.4% (6)
Redness	51.6% (33)	32.8% (21)	18.8% (12)	0	50.0% (32)	32.8% (21)	12.5% (8)	4.7% (3)
Pain	50.0% (32)	34.4% (22)	15.6% (10)	0	53.1% (34)	34.4% (22)	17.2% (11)	1.6% (1)
Discoloration	40.6% (26)	23.4% (15)	12.5% (8)	4.7% (3)	39.1% (25)	20.3% (13)	12.5% (8)	6.3% (4)
Itching	28.1% (18)	20.3% (13)	7.8% (5)	0	34.4% (22)	21.9% (14)	12.5% (8)	0

Table 6: Common Treatment Responses by Duration After Initial Treatment with EVOLYSSE™ SMOOTH and Control Occurring in > 5% of Treated Subjects (N = 64)

CTR	EVOLYSSE™ SMOOTH					Control				
	< 3 days % (n)	4 – 7 days % (n)	8 – 14 days % (n)	15 – 29 days % (n)	> 30 days % (n)	< 3 days % (n)	4 – 7 days % (n)	8 – 14 days % (n)	15 – 29 days % (n)	> 30 days % (n)
Tenderness	43.8% (28)	15.6% (10)	3.1% (2)	1.6% (1)	0	39.1% (25)	18.8% (12)	6.3% (4)	1.6% (1)	0
Swelling	31.3% (20)	15.6% (10)	7.8% (5)	1.6% (1)	0	34.4% (22)	15.6% (10)	10.9% (7)	1.6% (1)	0
Lumps	21.9% (14)	17.2% (11)	9.4% (6)	1.6% (1)	3.1% (2)	28.1% (18)	17.2% (11)	6.3% (4)	3.1% (2)	4.7% (3)
Bruising	18.8% (12)	15.6% (10)	12.5% (8)	4.7% (3)	0	21.9% (14)	18.8% (12)	9.4% (6)	4.7% (3)	0
Redness	34.4% (22)	14.1% (9)	0	1.6% (1)	1.6% (1)	35.9% (23)	10.9% (7)	0	3.1% (2)	0
Pain	40.6% (26)	6.3% (4)	3.1% (2)	0	0	39.1% (25)	10.9% (7)	3.1% (2)	0	0
Discoloration	21.9% (14)	6.3% (4)	9.4% (6)	3.1% (2)	0	15.6% (10)	10.9% (7)	7.8% ()5)	4.7% (3)	0
Itching	23.4% (15)	1.6% (1)	3.1% (2)	0	0	28.1% (18)	3.1% (2)	3.1% (2)	0	0

The severity and duration of CTRs reported by >5% of subjects after initial treatment with EVOLYSSE™ FORM are summarized in Table 7 and Table 8, respectively. The incidence and severity of CTRs were similar between the EVOLYSSE™ FORM and control NLFs with most CTRs reported as mild or moderate and resolving within 7 days. The incidence of CTRs was lower after retreatment with EVOLYSSE™ FORM.

Table 7: Common Treatment Responses by Maximum Severity After Initial Treatment with EVOLYSSE™ FORM and Control Occurring in > 5% of Treated Subjects (N = 66)

CTR	EVOLYSSE™ FORM				Control			
	Total % (n)	Mild % (n)	Moderate % (n)	Severe % (n)	Total % (n)	Mild % (n)	Moderate % (n)	Severe % (n)
Tenderness	75.8% (50)	47.0% (31)	25.8% (17)	3.0% (2)	71.2% (47)	42.4% (28)	25.8% (17)	3.0% (2)
Swelling	69.7% (46)	40.9% (27)	27.3% (18)	1.5% (1)	69.7% (46)	48.5% (32)	19.7% (13)	1.5% (1)
Bruising	60.6% (40)	27.3% (18)	28.8% (19)	4.5% (3)	56.1% (37)	30.3% (20)	24.2% (16)	1.5% (1)
Redness	57.6% (38)	34.8% (23)	19.7% (13)	3.0% (2)	48.5% (32)	27.3% (18)	21.2% (14)	0
Lumps	57.6% (38)	28.8% (19)	24.2% (16)	4.5% (3)	54.5% (36)	30.3% (20)	22.7% (15)	1.5% (1)
Pain	53.0% (35)	34.8% (23)	16.7% (11)	1.5% (1)	50.0% (33)	34.8% (23)	15.2% (10)	0
Discoloration	36.4% (24)	18.2% (12)	15.2% (10)	3.0% (2)	33.3% (22)	16.7% (11)	16.7% (11)	0

CTR	EVOLYSSE™ FORM				Control			
	Total % (n)	Mild % (n)	Moderate % (n)	Severe % (n)	Total % (n)	Mild % (n)	Moderate % (n)	Severe % (n)
Itching	28.8% (19)	21.2% (14)	6.1% (4)	1.5% (1)	31.8% (21)	27.3% (18)	4.5% (3)	0
Headache	6.1% (4)	6.1% (4)	0	0	6.1% (4)	6.1% (4)	0	0

Table 8: Common Treatment Responses by Duration After Initial Treatment with EVOLYSSE™ FORM and Control Occurring in > 5% of Treated Subjects (N = 66)

CTR	EVOLYSSE™ FORM					Control				
	< 3 days % (n)	4 – 7 days % (n)	8 – 14 days % (n)	15 – 29 days % (n)	> 30 days % (n)	< 3 days % (n)	4 – 7 days % (n)	8 – 14 days % (n)	15 – 29 days % (n)	> 30 days % (n)
Tenderness	47.0% (31)	15.2% (10)	12.1% (8)	1.5% (1)	0	47.0% (31)	13.6% (9)	9.1% (6)	1.5% (1)	0
Swelling	33.3% (22)	27.3% (18)	7.6% (5)	1.5% (1)	0	39.4% (26)	21.2% (14)	9.1% (6)	0	0
Bruising	18.2% (12)	21.2% (14)	18.2% (12)	1.5% (1)	1.5% (1)	15.2% (10)	21.2% (14)	18.2% (12)	1.5% (1)	0
Redness	33.3% (22)	10.6% (7)	13.6% (9)	0	0	25.8% (17)	12.1% (8)	10.6% (7)	0	0
Lumps	24.2% (16)	3.0% (2)	16.7% (11)	10.6% (7)	3.0% (2)	28.8% (19)	9.1% (6)	10.6% (7)	3.0% (2)	3.0% (2)
Pain	36.4% (24)	9.1% (6)	7.6% (5)	0	0	31.8% (21)	12.1% (8)	6.1% (4)	0	0
Discoloration	12.1% (8)	9.1% (6)	13.6% (9)	1.5% (1)	0	13.6% (9)	9.1% (6)	9.1% (6)	1.5% (0)	0
Itching	15.2% (10)	9.1% (6)	1.5% (1)	3.0% (2)	0	21.2% (14)	9.1% (6)	1.5% (1)	0	0
Headache	6.1% (4)	0	0	0	0	6.1% (4)	0	0	0	0

An Adverse Event (AE) was defined as an untoward medical occurrence which did not necessarily have a causal relationship to the study device. The AE was considered related to the study device if a causal relationship was at least a reasonable possibility.

Of the 70 subjects in the EVOLYSSE™ SMOOTH arm, 5 subjects (7.1%) had 10 treatment-related AEs in the EVOLYSSE™ SMOOTH NLF and 6 subjects (8.6%) had 14 treatment-related AEs in the control NLF after initial treatment. All AEs were mild or moderate and required no action to be taken. Most AEs resolved within 1 month. The treatment-related AEs in the EVOLYSSE™ SMOOTH NLF were injection site discoloration (3 subjects), injection site mass (2 subjects), injection site erythema (2 subjects), injection site bruising (1 subject), injection site pain (1 subject), and flushing (1 subject). Among the 44 subjects who received retreatment with EVOLYSSE™ SMOOTH, 3 subjects (6.8%) had 5 treatment-related AEs, which included mild injection site bruising (1 subject in both NLFs), swelling (1 subject), pain (1 subject), and mass

(1 subject). These AEs all resolved without any action to be taken.

Of the 70 treated in the EVOLYSSE™ FORM arm, 11 subjects (15.7%) had 18 treatment-related AEs in the EVOLYSSE™ FORM NLF and 8 subjects (11.4%) had 13 treatment-related AEs in the control NLF after initial treatment. Most AEs were mild, required no action to be taken, resolved within 2 months. The most common treatment-related AEs in the EVOLYSSE™ FORM NLF were injection site mass (6 subjects), injection site discoloration, injection site pain, and injection site pruritis (2 subjects each). Injection site swelling, injection site bruising, facial discomfort, sensation of a foreign body, headache, and skin swelling were also reported in 1 subject each. Among the 47 subjects who received retreatment with EVOLYSSE™ FORM, 2 subjects (4.3%) had 2 treatment-related AEs, which included mild injection site pain (1 subject) and mild headache (1 subject) which resolved without any action taken.

There were no treatment-related serious AEs in the study.

2. Effectiveness Results

EVOLYSSE™ SMOOTH Arm

The primary endpoint was met. Based on the IPR results using the WSRS, the difference in change from baseline was in favor of EVOLYSSE™ SMOOTH versus control at 6 months, -0.2 (95% CI [-0.416, -0.019]), and the upper confidence interval did not cross the non-inferiority margin of a 0.5 grade change. The corresponding p-value was < 0.001.

The IPR responder rates at 6 months for Evolysse™ SMOOTH and control are shown in Table 9. The IPR responder rates are expected to be lower than live assessments due to the challenges and limitations of evaluating changes in wrinkle severity via 2D photographs.

Table 9: WSRS IPR Responder Rates at Month 6

Evolysse™ SMOOTH	Control
51.6% (32/62)	35.5% (22/62)

Throughout the 12-month follow-up period (Table 10) EVOLYSSE™ SMOOTH continued to provide a clinically significant improvement in wrinkle severity with most NLFs maintaining improvement through 12 months [64.6% (42/65)].

At Month 6, the GAIS responder rate was 98.4% (61/62) based on BLE assessments and 95.2% (59/62) based on the subject assessments. At 1 year, the BLE GAIS responder rate was 66.2% (43/65) and the subject GAIS responder rate was 92.3% (60/65).

Table 10: Effectiveness Results through 1 Year (mITT)

Visit	WSRS Responder Rate % (n/N)	GAIS Responder Rate % (n/N)	
		BLE	Subject
Month 3	92.3% (60/65)	95.4% (62/65)	96.9% (63/65)
Month 6	93.5% (58/62)	98.4% (61/62)	95.2% (59/62)
Month 9	80.3% (49/61)	88.5% (54/61)	83.6% (51/61)
Month 12	64.6% (42/65)	66.2% (43/65)	92.3% (60/65)

The mean score on the Appraisal of Nasolabial Folds module of the FACE-Q questionnaire for the EVOLYSSE™ SMOOTH group improved from 34.1 at baseline to 65.3 at 6 months and 56.6 at 12 months. These improved scores indicate that subjects were satisfied with the appearance of their NLFs after treatment with EVOLYSSE™ SMOOTH compared to baseline.

EVOLYSSE™ FORM Arm

The primary endpoint was met. Based on the IPR results using the WSRS, the difference in change from baseline was in favor of EVOLYSSE™ FORM versus control at 6 months, -0.3 (95% CI [-0.500, -0.032]), and the upper confidence interval did not cross the non-inferiority margin of a 0.5 grade change. The corresponding p-value was < 0.001. The IPR responder rates at 6 months for Evolysse™ FORM and control are shown in Table 11. The IPR responder rates are expected to be lower than live assessments due to the challenges and limitations of evaluating changes in wrinkle severity via 2D photographs.

Table 11: WSRS IPR Responder Rates at Month 6

Evolysse™ FORM	Control
45.2% (28/62)	38.7% (24/62)

Throughout the 12-month follow-up period (Table 12), EVOLYSSE™ FORM continued to provide a clinically significant improvement in wrinkle severity with most NLFs maintaining improvement through 12 months [72.1% (44/61)].

At Month 6, the GAIS responder rate was 95.2% (60/63) based on BLE assessments and 88.9% (56/63) based on the subject assessments. At 1 year, the BLE GAIS responder rate was 73.8% (45/61) and the subject GAIS responder rate was 80.3% (49/61).

Table 12: Effectiveness Results through 1 Year (mITT)

Visit	WSRS Responder Rate % (n/N)	GAIS Responder Rate % (n/N)	
		BLE	Subject
Month 3	95.4% (62/65)	96.9% (63/65)	95.4% (62/65)
Month 6	92.1% (58/63)	95.2% (60/63)	88.9% (56/63)
Month 9	83.1% (49/59)	83.1% (49/59)	83.3% (50/60)
Month 12	72.1% (44/61)	73.8% (45/61)	80.3% (49/61)

The mean score on the Appraisal of Nasolabial Folds module of the FACE-Q questionnaire for the EVOLYSSE™ FORM group improved from 31.5 at baseline to 65.4 at 6 months and 52.4 at 12 months. These improved scores indicate that subjects were satisfied with the appearance of their NLFs after treatment with EVOLYSSE™ FORM compared to baseline.

3. Subgroup Analyses

   The following baseline characteristics were evaluated for potential association with safety and effectiveness outcomes: sex, race, ethnicity, age, Fitzpatrick skin type, injection volume, baseline WSRS score, touch-up status, investigational site, and needle size.

   The incidence of treatment-related AEs was higher after treatment with EVOLYSSE™ FORM using 27G needles (22.0%, 9/41) versus 30G needles (7.0%, 3/43). No negative correlations for safety outcomes (CTRs and treatment-related AEs) were observed with any other subgroup. The effectiveness subgroup analyses for mean change from baseline at 6 months (primary timepoint) based on live, masked evaluator assessments using the WSRS ranged from -0.8 to -2.0 demonstrating clinically meaningful improvement in all subgroups.

   The results of these analyses support the safety and effectiveness across these various subgroups.

   The study was not specifically powered for sex, race, ethnicity, age, or Fitzpatrick skin type subgroups.

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 13 investigators (6 treating investigators and 7 blinded evaluators). None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

A. European Clinical Study CLIN1901

EVOLYSSE™ SMOOTH was evaluated for the correction of facial wrinkles and folds in a prospective, interventional, multicenter study conducted in France. A total of 61 subjects received treatment in the NLFs and perioral lines with follow-up through 12 months.

1. Safety Results
   After treatment, subjects recorded injection site reactions (ISRs) for 30 days. The intensity of ISRs after treatment with EVOLYSSE™ SMOOTH in the NLFs and perioral lines is shown in Table 13. Most ISRs were slight or moderate in intensity and resolved within the 30-day diary period.

Table 13: Injection Site Reactions by Maximum Intensity After Treatment with EVOLYSSE™ SMOOTH (N = 61)

ISR – NLFs	Total % (n)	Slight % (n)	Moderate % (n)	Severe % (n)
Swelling - Edema	47.5%(29)	29.5% (18)	14.8% (9)	3.3% (2)
Ecchymosis - Bruising	47.5% (29)	23.0% (14)	19.7% (12)	4.9% (3)
Induration - Firmness	41.0% (25)	31.1% (19)	8.2% (5)	1.6% (1)
Lumps/Bumps - Irregularity	39.3% (24)	21.3% (13)	16.4% (10)	1.6% (1)
Pain - Tenderness	27.9% (17)	21.3% (13)	4.9% (3)	1.6% (1)
Redness	24.6% (15)	18.0% (11)	6.6% (4)	0
Itching - Pruritus	9.8% (6)	9.8% (6)	0	0
Discoloration	6.6% (4)	6.6% (4)	0	0
ISR – Perioral Lines	**Total % (n)**	**Slight % (n)**	**Moderate % (n)**	**Severe % (n)**
Swelling - Edema	60.7% (37)	31.1% (19)	23.0% (14)	6.6% (4)
Ecchymosis - Bruising	45.9% (28)	18.0% (11)	21.3% (13)	6.6% (4)
Induration - Firmness	44.3% (27)	24.6% (15)	18.0% (11)	1.6% (1)
Lumps/Bumps - Irregularity	34.4% (21)	16.4% (10)	14.8% (9)	3.3% (2)
Pain - Tenderness	50.8% (31)	36.1% (22)	11.5% (7)	3.3% (2)
Redness	27.9% (17)	19.7% (12)	6.6% (4)	1.6% (1)
Itching - Pruritus	8.2% (5)	8.2% (5)	0	0
Discoloration	11.5% (7)	9.8% (6)	1.6% (1)	0

Of the 61 subjects treated with EVOLYSSE™ SMOOTH, 2 subjects (3.3%) had 3 treatment-related AEs, which included headache and induration. These AEs were all slight (mild) in intensity and resolved without sequelae.

2. Effectiveness Results

The Investigators assessed wrinkle severity of the NLFs and perioral lines using the 6-point Lemperle Rating Scale (LRS). Most subjects showed a clinically significant improvement (i.e., ≥ 1-point improvement) in wrinkle severity through 12 months after treatment with EVOLYSSE™ SMOOTH (Table 14).

Table 14: Investigator LRS Responder Rates (N = 61)

Timepoint	NLF Responder Rate % (n)	Perioral Lines Responder Rate % (n)
Day 30	98.4% (60)	93.4% (57)
Month 3	83.6% (51)	91.8% (56)
Month 6	77.0% (47)	86.9% (53)
Month 9	65.0% (39)	81.7% (49)
Month 12	54.1% (33)	73.8% (45)

XII. 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.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The effectiveness conclusions were drawn based upon the US pivotal study. EVOLYSSE™ SMOOTH and EVOLYSSE™ FORM were shown to be effective for correction of NLFs, with results lasting for 1 year:

- The primary endpoint was met: at 6 months the WSRS mean change from baseline as rated by IPR was in favor of EVOLYSSE™ SMOOTH and EVOLYSSE™ FORM and was non-inferior to control (non-inferiority margin a 0.5 grade change)
- Over 90% of the EVOLYSSE™ SMOOTH and EVOLYSSE™ FORM NLFs were responders on the WSRS at 6 months as rated by the BLEs, and improvements in NLF severity lasted through 1 year after treatment
- 90% or more of subjects had overall aesthetic improvement at 6 months after EVOLYSSE™ SMOOTH and EVOLYSSE™ FORM treatment based on BLE and subject GAIS assessment of the NLFs, and improvements lasted through 1 year after treatment
- Subject appraisal of NLFs showed significant improvement from baseline ($p < 0.0001$) at all timepoints through 1 year on the FACE-Q Appraisal of NLFs questionnaire

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in a clinical study conducted to support PMA approval as described

above. EVOLYSSE™ SMOOTH and EVOLYSSE™ FORM were shown to be safe for correction of NLFs:

- For initial and retreatments, most CTRs were mild or moderate in severity and resolved within 1 week
- The most common CTRs were injection site swelling and tenderness
- The most common treatment-related AEs after initial treatment were injection site discoloration, injection site mass, and injection site erythema for EVOLYSSE™ SMOOTH and injection site mass for EVOLYSSE™ FORM, and all other AEs occurred in no more than 2 subjects each
- Most treatment-related AEs were mild in severity
- There were no treatment-related SAEs

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The clinical benefit of EVOLYSSE™ SMOOTH and EVOLYSSE™ FORM for correction of dynamic facial wrinkles and folds was demonstrated based on blinded evaluator assessments and patient reported outcomes from the CLIN2101 study.

- The primary endpoint was met. Based on the IPR results, the difference in change from baseline was in favor of EVOLYSSE™ SMOOTH versus control at 6 months, -0.2 (95% CI [-0.416, -0.019]), and the upper confidence interval did not cross the non-inferiority margin of a 0.5 grade change. The corresponding p-value was < 0.001.
- The primary endpoint was met. Based on the IPR results, the difference in change from baseline was in favor of EVOLYSSE™ FORM versus control at 6 months, -0.3 (95% CI [-0.500, -0.032]), and the upper confidence interval did not cross the non-inferiority margin of a 0.5 grade change. The corresponding p-value was < 0.001.
- Across all measures, similar or better effectiveness results were observed for EVOLYSSE™ SMOOTH and EVOLYSSE™ FORM compared to the FDA-approved control.
- Most treatment NLFs in the EVOLYSSE™ SMOOTH and EVOLYSSE™ FORM arms were responders on the WSRS (i.e., ≥ 1-point improvement) through 12 months with higher responder rates observed compared to the control NLFs.
- The BLEs and subjects rated most treatment and control NLFs in the EVOLYSSE™ SMOOTH and EVOLYSSE™ FORM arms as responders on the GAIS through 12 months.
- Subjects in the EVOLYSSE™ SMOOTH and EVOLYSSE™ FORM arms reported a statistically significant improvement in mean scores on the FACE-Q Appraisal of Nasolabial Folds questionnaire for both their treatment and control NLFs through 12 months, indicating that they were satisfied with the appearance of their NLFs.

The probable risks of the device are also based on data collected in a clinical study

conducted to support PMA approval as described above.

1. Patient Perspective
   Patient perspectives considered during the review included:
   - Most subjects rated improvement on the GAIS after treatment with EVOLYSSE™ SMOOTH and EVOLYSSE™ FORM through 12 months
   - The mean scores on the FACE-Q Appraisal of Nasolabial Folds questionnaire showed improvement through 12 months indicating that subjects were satisfied with the appearance of their NLFs after treatment with EVOLYSSE™ SMOOTH and EVOLYSSE™ FORM compared to baseline

In conclusion, given the available information above, the data support that the probable benefits outweigh the probable risks for EVOLYSSE™ SMOOTH and EVOLYSSE™ FORM for dermal and subdermal injection to correct dynamic facial wrinkles and folds (such as NLFs).

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The data demonstrate the benefits of EVOLYSSE™ SMOOTH and EVOLYSSE™ FORM for dermal and subdermal injection to correct dynamic facial wrinkles and folds (such as NLFs) outweigh the risks and the intended patient population will achieve clinically significant results. The benefits and risks of dermal fillers are sufficiently well understood for patients to make informed decisions about their use.

XIV. CDRH DECISION

CDRH issued an approval order on February 13, 2025. The final clinical conditions of approval cited in the approval order are described 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	V1	V1 Phone f/u	V2	V2 Phone f/u	V3	V4
Week	W0	72hrs	W2	72hrs	W4	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.

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

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.