SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Injectable Dermal Filler

Device Trade Name: Bellafill

Applicant's Name and Address: Suneva Medical, Inc.
5879 Pacific Center Boulevard
San Diego, CA 92121

Date of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P020012/s09

Date of FDA Notice of Approval: December 23, 2014

Expedited: Not applicable

The original PMA (P020012) for Bellafill (previously named Artefill) was approved for mid-to-deep dermal implantation for the correction of nasolabial folds. The SSED to support the correction of nasolabial folds indication is available on the CDRH website and is incorporated by reference. The purpose of this supplement is to add "correction of moderate to severe, atrophic, distensible facial acne scars on the cheek in patients over the age of 21 years" as a new Indication for Use.

II. INDICATIONS FOR USE

Bellafill is indicated for the correction of nasolabial folds and moderate to severe, atrophic, distensible facial acne scars on the cheek in patients over the age of 21 years.

III. CONTRAINDICATIONS

- Bellafill is contraindicated for patients displaying a positive response to the required Bellafill Skin Test. Refer to the Bellafill Skin Test Instructions for Use for complete instructions for administration and evaluation of the skin test.
- Bellafill is contraindicated for patients with severe allergies manifested by a history of anaphylaxis, or history or presence of multiple severe allergies.
- Bellafill contains lidocaine and is contraindicated for patients with known lidocaine hypersensitivity.
- Bellafill contains bovine collagen and is contraindicated for patients with a history of allergies to any bovine collagen products, including but not limited to injectable collagen, collagen implants, hemostatic sponges, and collagen-based sutures, because these patients are likely to have hypersensitivity to the bovine collagen in Bellafill.

- Bellafill is contraindicated for patients undergoing or planning to undergo desensitization injections to meat products, as these injections can contain bovine collagen.
- Bellafill is contraindicated for patients with bleeding disorders.
- Bellafill is contraindicated for use in lip augmentation and injection into the vermilion or the wet mucosa of the lip.
- Bellafill should not be used in patients with known susceptibility to keloid formation or hypertrophic scarring.

IV. WARNINGS AND PRECAUTIONS

The Warnings and Precautions can be found in the Bellafill labeling.

V. DEVICE DESCRIPTION

Bellafill is a suspension of non-resorbable polymethylmethacrylate (PMMA) microspheres, 30 to 50 microns in diameter, suspended in an aqueous solution of 3.5% bovine collagen, 92.6% buffered, isotonic water for injection, 0.3% lidocaine hydrochloride, 2.7% phosphate buffer, and 0.9% sodium chloride.

Bellafill is packaged in heat sealed thermoform trays and placed in an outer carton of heavy paper stock. The Bellafill product tray is packaged with 5 x 0.8 cc filled 1 cc syringes, patient chart labels and the appropriate needles for injection (i.e. 26G). Each syringe has a tamper evident seal over the end-cap of the syringe. Syringes provide the primary sterile container/closure system.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Treatments for facial scarring include chemical peels, dermabrasion (including microdermabrasion and traditional dermabrasion), laser resurfacing (ablative and non-ablative), dermal fillers, and surgery (i.e., excisions).

VII. MARKETING HISTORY

Bellafill has been sold in the United States since FDA approval on October 27, 2006. Bellafill has been commercially available in Canada since June 6, 2011 and in Korea and Singapore since July 2013. Bellafill has not been removed from the marketplace for any reasons related to safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The safety of Bellafill for correction of moderate to severe, atrophic, distensible facial acne scars on the cheek in patients over 21 years of age was evaluated in a premarket study. Potential adverse effects (e.g., complications) associated with the use of the device, as reported in the clinical study were implant site mass, injection site pain, swelling, injection site bruising, tenderness and injection site reactions, (i.e., lumpiness and papule formation).

Post-Market Surveillance

Since product approval, the adverse events received via post-marketing surveillance of Bellafill in on-label or off-label settings have been infrequent. For more information, please see Section X. "Summary of Supplemental Clinical Information."

SUMMARY OF PRECLINICAL STUDIES

The preclinical testing performed in the original P020012 application was adequate to support the safety and effectiveness of the device for the correction of moderate to severe, atrophic, distensible facial acne scars on the cheek in patients over 21 years of age. No additional preclinical studies were submitted in this Panel Track Supplement.

IX. SUMMARY OF PRIMARY CLINICAL STUDY

The sponsor, i.e., Suneva Medical, Inc. performed a clinical study to establish a reasonable assurance of safety and effectiveness for Bellafill in the correction of moderate to severe, atrophic, distensible facial acne scars on the cheek in patients over the age of 21 years.

A. Study Design

Patients were enrolled and treated between February 23, 2012 and January 31, 2013. The database for this PMA reflects data collected through February 28, 2014 and includes 175 subjects who were randomized and 147 patients who received either Bellafill or Control treatment. There were 10 investigational sites in the U.S.

The clinical Study (SUN-11-001) was a prospective, randomized, multi-center, evaluator-blind study of subjects over the age of 21 for correction of moderate to severe, atrophic, distensible facial acne scars on the cheek. Subjects who met all inclusion/exclusion criteria were randomized (2:1) to Bellafill or Control (i.e., sterile saline for injection). Randomization included stratification by study site for gender and Fitzpatrick skin type. The study included 67 subjects with Fitzpatrick skin types IV, V and VI. Prior to treatment, patients were skin tested to determine possible sensitivity to bovine collagen.

The primary safety objective was to identify the incidence of all adverse events for 12 months following treatment.

The primary effectiveness endpoint was the success rate at 6 months based on blinded evaluator assessment using the validated 4 point Acne Scar Rating Scale (ASRS) with success defined as at least a 2 point improvement on the ASRS for at least 50% of a patient's treated scars.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in Study SUN-11-001 was limited to subjects who met the following inclusion criteria: male or female of any race 18 years of age or older. Females of childbearing potential had to have a negative urine pregnancy test result at baseline and practice a reliable method of contraception throughout the study. All subjects needed to display moderate to severe atrophic acne scars (treatment scars) on the cheek(s) and had to meet the following criteria: greater than four treatment scars that were grade 3 or 4 on the validated 4-point Acne Scar Rating Scale (ASRS); all scars had to be sufficiently distant from one another to allow independent treatment and grading using the ASRS; treatment scars had to be depressed rolling scars with rounded borders (i.e., soft-contoured); treatment scars had to be distensible, and not significantly hypo- or hyperpigmented; treatment scars had to have no underlying papules or nodules; and icepick, boxcar or bound down acne scars could not be included in treatable scars, but could be present in the treatment area, a desire for correction of moderate to severe acne scarring, willingness to withhold additional aesthetic therapies to the face (e.g., other soft tissue fillers and/or any resurfacing procedures) for the duration of the study, be able to follow study instructions and likely to complete all required visits, and sign the IRB-approved Informed Consent form, Photographic Release Form as well as the Authorization for Use and release of Health and Research Study Information (HIPAA) forms prior to any study-related procedures being performed.

Patients did not enroll in Study SUN-11-001 if they met any of the following exclusion criteria: pregnant or breast-feeding subjects or patients who were of childbearing potential and not practicing a reliable method of birth control, patients who had undergone treatment of acne scars with any of the prohibited treatment/procedures and/or use of any other prohibited treatment/procedure within the time periods as listed in protocol, patients with any skin pathology or condition that could interfere with the evaluation of the treatment areas, or worsen due to the proposed treatment or require interfering topical, systemic or surgical therapy, subjects with a recent or current history of inflammatory skin disease, infection, cancerous/pre-cancerous lesion, and patients with an unhealed wound or clinically significant acne in the treatment areas. Clinically significant acne was defined as a patient whom has greater than three active inflammatory acne lesions in either the left or right treatment area, patients with a history of systemic granulomatous diseases (e.g., Sarcoid, Wegeners, TB, etc.) or connective tissue diseases (e.g., lupus, dermatomyositis, etc.), subjects with hypertrophic acne scars, any evidence of keloid scarring, predominantly icepick scarring or sinus tract scars, patients with numerous eligible acne scars in the treatment area such that the eligible scars could not be individually identified and mapped, subjects with a known hypersensitivity or previous allergic reaction to any of the components of the study device (including lidocaine or any amide-based anesthetic), or a history of allergies to any bovine collagen product, including but not limited to injectable collagen, collagen implants, hemostatic sponges, and collagen-based sutures, patients who were undergoing or planned to undergo desensitization injections to meat products, subjects who were unable to communicate or cooperate with the Investigator due to a language barrier (non-English speaking), poor mental development, or impaired cerebral function, patients with evidence of alcohol or drug abuse, or history of poor cooperation, non-compliance with medical treatment, or unreliability, subjects who used of an investigation device, biologic or drug in the past 30 days, or were currently participating in an experimental drug, biologic or device trial, patients who had excisional facial surgery (e.g., Blepharoplasty, Face Lift, Rhinoplasty) of the face less than one year prior to study enrollment or plans for facial surgery during the study, subjects who exhibit

additional physical attributes that prevent assessment or treatment of acne scars, as judged by the blinded Evaluator, (such as excessive facial hair, traumatic or surgical facial scars, excessive hyperpigmentation in the treatment area), patients with a condition or in a situation that, in the Investigator's opinion, may have put the subject at significant risk, may have confounded the study results, or may have interfered significantly with the subject's participation in the study and/or an employee (or relative of an employee) of the Investigator, Sponsor or representative of the Sponsor.

2. Follow-up Schedule

Pre-Treatment evaluations included a skin test against bovine collagen and assessment of study entry criteria and medical history, as well as scoring acne scar severity and patient photography.

Subjects who did not display an immune response against the Bellafill skin test were enrolled and injected with either Bellafill or Control (sterile saline for injection). Patient follow-up included telephone contact at 72 hours after each treatment and clinical visits at weeks 2, 4 (with touch-up if needed), 6, and 8 after treatment as well as months 3 and 6. For subjects initially randomized to Bellafill follow-up also occurred at months 9 and 12. Subjects initially randomized to Control, could elect to receive open-label Bellafill injections at the 6 Month visit with subsequent follow-ups at 72 hours (by telephone) and clinical visits at week 2 and 4 (with touch-up if needed) as well as weeks 6, and 8 and months 3, 6, 9 and 12. Safety assessments also included subjects recording adverse outcomes in a 14 day post injection diary.

Post-Treatment, the parameters measured were: 1) a Blinded Evaluator's determination of acne scar appearance via a 4-point validated Acne Scar Rating Scale (ASRS); 2) a Treating Investigator's assessment of safety outcomes at each visit; 3) Blinded Evaluators' assessment of patient appearance using the Global Aesthetic Improvement Scale (PGAIS); 4) a subject's completion of a 14 day treatment diary (after each injection for recording adverse patient outcomes) as well as 5) their evaluation of general appearance using a Global Aesthetic Improvement Scale (SGAIS) and 6) a subject's assessment of scar correction (SASC). Finally, 7) an independent masked three-person panel review of photographs was performed to evaluate clinical outcomes and correlation with the ASRS and PGAIS outcomes from the Month 6 visit.

3. Clinical Endpoints

The primary safety objective was to identify the incidence of all adverse events including subject adverse outcomes recorded during the first fourteen days after treatment (in a subject diary) and Treating Investigator safety assessments (i.e., adverse events) at a 72 hour telephone call and clinic visits at weeks 2, 4, 6, and 8, as well as months 3, 6, 9 and 12. Subjects in the Control group who received Bellafill injections after the Month 6 assessment were followed in a similar manner for 12 months.

The primary effectiveness endpoint was the success rate at 6 months based on the validated 4 point Acne Scar Rating Scale (ASRS) in Table 1 as determined by Blinded Evaluators' assessment. For each subject, success was defined as at least a 2 point improvement for at least 50% of the treated scars.

Table 1. Acne Scar Rating Scale (ASRS)

Score	Description
1	**Minimal or None -** Depth up to 0.5mm in depth. Visibility = Perceptible with tangential lighting
2	**Mild -** Depth >0.5mm to <1.5mm in depth. Visibility = Moderately Detectable with tangential lighting
3	**Moderate -** Depth = ≥1.5mm to <2.5mm in depth. Visibility = Easily seen with tangential lighting
4	**Severe -** Depth = ≥2.5 mm in depth. Visibility = Substantial shadowing with tangential lighting

The following additional effectiveness endpoints were evaluated: 1) Blinded Evaluator ASRS score at Weeks 2, 4, 6, and 8, and Months 3, 9 and 12 after treatment, 2) Blinded Evaluator PGAIS (Table 2), 3) Masked SASC (Table 3) and SGAIS (Table 4) (compared baseline photographs) and 4) Independent Masked Photographic Review.

Table 2. Physician Global Aesthetic Improvement Scale (PGAIS)

Rating	Description
5 = Much improved	Marked improvement in appearance from the initial condition, touch-up treatment(s) is not indicted
4 = Improved	Obvious improvement in appearance from the initial condition, but a touch-up or re-treatment is indicated
3 = No Change	The appearance is essentially the same as the original condition
2 = Worse	The appearance is worse than the original condition
1 =Much Worse	The appearance is much worse than the original condition

Table 3. Subject Assessment of Scar Correction (SASC)

Rating	Description
6	Very Satisfied
5	Satisfied
4	Somewhat Satisfied
3	Somewhat Dissatisfied
2	Dissatisfied
1	Very Dissatisfied

Table 4. Subject Global Aesthetic Improvement Scale (SGAIS)

Rating	Description
5 = Much improved	Marked improvement in appearance from the initial condition
4 = Improved	Obvious improvement in appearance from the initial condition
3 = No change	The appearance is essentially the same as the original condition
2 = Worse	The appearance is worse than the original condition
1 = Much Worse	The appearance is much worse than the original condition

B. Accountability of PMA Cohort

Table 5 presents the number of subjects involved in the study as a function of time and the reasons for patients leaving the study.

Table 5. Accountability of the PMA Cohort

Patient Population	**Number of Subjects** (Reasons for subject loss)	**Number of Control Subjects** (Reasons for subject loss)
Patients Screened	**199**	
Patients Randomized to Treatment	**175** (24 screened patients were not randomized (i.e., 23 failed entry criteria and one withdrew consent)	
Patients Receiving Treatment	**147 Total = 97 Bellafill subjects** (28 randomized subjects did not receive treatment - 8 lost to follow-up, 10 withdrew consent, 3 positive skin tests, 5 failed entry criteria, 1 moved out of town and 1 sponsor decision).	**50 Control subjects**
Patients Completing 6 Month Visit	**87/97 (90%) Bellafill subjects** (8 lost to follow-up, 5 withdrew consent and 1 did not wish to participate)	**46/50 (92%) Control subjects** (2 lost to follow-up, 1 withdrew consent and 1 scheduling conflict.)
Control Subjects treated with Bellafill at 6 Month		**46 Control subjects** received Bellafill injections at Month 6
Patients Completing the Study (i.e., 12 Month Follow-up after Bellafill injection)	**83/97 (86%) Bellafill subjects** (3 lost to follow-up and 1 withdrew consent)	**42/50 (91%) Control subjects** (2 lost to follow-up and 2 withdrew consent)
Scars per cohort	789 Scars (97 subjects) were treated with Bellafill	397 scars (50 subjects) were treated with Control

In this study 87 Bellafill and 46 Control subjects were evaluated at the Month 6 visit for the primary effectiveness endpoint. Because Control subjects could receive Bellafill injections at the 6 Month visit (with 12 month follow-up), and because the adverse event profile for the 46/50 Control subjects who received Bellafill injections was similar to the 97 subjects initially randomized to Bellafill injections, the safety data presented in this Summary reflect the combination of patient outcomes for the initial (n=97) and cross-over (n=46) Bellafill subjects (i.e., 97 + 46 = 143 total) compared to the 50 subjects who initially received Control treatment.

C. Study Population Demographics and Baseline Parameters

The Bellafill and Control groups were well balanced with regard to demographics and baseline characteristics (Table 6). The mean age was 44.6 in the Bellafill group and 45.3 in the Control group. The study enrolled a substantial portion of males (i.e., 38.1% in Bellafill and 40.0% in Control groups) as well as subjects with Fitzpatrick skin types V and VI (i.e., 25% in Bellafill

and 20% in Control groups). The demographics for patients with Fitzpatrick Skin Types IV - VI and patients under the age of 36 were similar to the general study population.

Table 6. Subject Demographics – Safety Population

Variable	**Bellafill** n=97	**Control** n=50
Age (years)		
Mean ± SD	44.6 ± 10.0	45.3 ± 10.7
Median (P25, P75)	45.0 (37.0, 52.0)	46.5 (37.0, 54.0)
Min, Max	21.0, 67.0	22.0, 63.0
Gender		
Male	37 (38.1%)	20 (40.0%)
Female	60 (61.9%)	30 (60.0%)
Race		
Caucasian	70 (72.2%)	38 (76.0%)
Black	20 (20.6%)	8 (16.0%)
American Indian/Native Alaskan	2 (2.1%)	0 (0.0%)
Native Hawaiian/Pacific Islander	1 (1.0%)	0 (0.0%)
Asian	4 (4.1%)	4 (8.0%)
Other	0 (0.0%)	0 (0.0%)
Ethnicity		
Hispanic/Latino	20 (20.6%)	13 (26%)
Not Hispanic/Latino	77 (79.4%)	37 (74.0%)
Fitzpatrick Skin Type		
I	4 (4.1%)	2 (4.0%)
II	30 (30.9%)	12 (24.0%)
III	18 (18.6%)	14 (28.0%)
IV	20 (20.6%)	12 (24.0%)
V	14 (14.4%)	6 (12.0%)
VI	11 (11.3%)	4 (8.0%)
No. of qualified scars/ subject		
Mean (SD)	8.9 +/- 4.6	8.4 +/- 3.7
Median (P25, P75)	8.0 (5.0, 11.0)	8.0 (5.0, 11.0)
Min, Max	4.0, 23.0	4.0, 17.0
Mean Scar Severity		
Mean (SD)	3.3 +/- 0.3	3.3 +/- 0.3
Median (P25, P75)	3.2 (3.0, 3.4)	3.2 (3.0, 3.5)
Min, Max	3.0, 4.0	3.0, 4.0

Injected Volumes of Bellafill and Control Correction:

All qualifying scars in both treatment groups received an initial injection. Touch-up treatments were given to 83.1% and 88.2% of the Bellafill and Control scars, respectively and 82.5% of the Bellafill and 82.0% of the Control subjects.

The average volume injected per subject in the initial injection was 0.93 mL and 1.53 mL in the Bellafill and Control groups, respectively. The average touch-up volume injected per subject was 0.69 mL and 1.32 mL in the Bellafill and Control groups, respectively. The average total volume injected per subject (initial + touch-up) was 1.50 mL and 2.61 mL in the Bellafill and Control groups, respectively, with a maximal volume received by an individual subject being 5.80 mL and 8.00 mL, for Bellafill and Control, respectively. The increased injection volume for the Control patients was not unexpected as saline infiltrates into tissue and is not expected to perform a dermal filler function for scar correction.

The average volume initially injected per scar was 0.11 mL and 0.18 mL in the Bellafill and Control groups, respectively. The average touch-up volume per scar was 0.10 mL and 0.17 mL in the Bellafill and control groups, respectively. The average total volume injected per scar (initial + touch-up) was 0.17 mL and 0.30 mL in the Bellafill and control groups, respectively with a maximal volume injected into an individual scar of 0.42 mL and 0.80 mL, respectively.

D. Safety and Effectiveness Results

1. Safety Results

Physician Diagnosed Adverse Events:

46/143 of the Bellafill and 16/50 of the Control subjects experienced at least one all cause (related and unrelated) Treatment-Emergent Adverse Event (TEAEs). TEAEs that occurred in ≥ 4% of the subjects (related and unrelated) (i.e., 51/143 of the Bellafill and 12/50 of the Control subjects) are presented below in Table 7.

Table 7. Treatment-Emergent AEs in ≥ 4% of the subjects sorted by system organ class (SOC) and preferred term

System organ class code	Preferred Term (PT)	Bellafill n=143*		Control n=50	
		Subjects	**Events**	**Subjects**	**Events**
General disorders and administration site conditions		**22 (15.4%)**	**27**	**1 (2.0%)**	**1**
Burning sensation		1 (0.7%)	1	0 (0.0)	0
Device breakage		1 (0.7%)	1	0 (0.0)	0
Fatigue		2 (1.4%)	2	0 (0.0)	0
Injection site bruising		3 (2.1%)	3	0 (0.0)	0
Implant site mass		1 (0.7%)	1	0 (0.0)	0
Injection site discoloration		1 (0.7%)	1	0 (0.0)	0
Injection site pain		3 (2.1%)	3	0 (0.0)	0
Injection site reactions		6 (4.2%)	6	0 (0.0)	0
Pruritus		1 (0.7%)	1	0 (0.0)	0
Swelling		3 (2.1%)	3	0 (0.0)	0

Tenderness	5 (3.5%)	5	1 (2.0%)	1
Infections and infestations	**14 (9.8%)**	**16**	**4 (8.0%)**	**6**
Bacterial infection	1 (0.7%)	1	0 (0.0)	0
Bronchitis	0 (0.0)	0	1 (2.0%)	1
Ear infection	1 (0.7%)	1	0 (0.0)	0
Hordeolum	1 (0.7%)	1	0 (0.0)	0
Influenza	1 (0.7%)	1	0 (0.0)	0
Influenza like illness	2 (1.4%)	2	2 (4.0%)	3
Meningitis	1 (0.7%)	1	0 (0.0)	0
Nasopharyngitis	4 (2.8%)	4	0 (0.0)	0
Oral infection	0 (0.0)	0	1 (2.0%)	1
Pharyngitis	1 (0.7%)	1	0 (0.0)	0
Pharyngitis streptococcal	1 (0.7%)	1	1 (2.0)	1
Sinusitis	2 (1.4%)	2	0 (0.0)	0
Skin papilloma	1 (0.7%)	1	0 (0.0)	0
Musculoskeletal and connective tissue disorders	**5 (3.5%)**	**5**	**5 (10.0%)**	**5**
Arthralgia	2 (1.4%)	2	0 (0.0)	0
Back pain	2 (1.4%)	2	2 (4.0%)	2
Hand fracture	0 (0.0)	0	1 (2.0%)	1
Pain in extremity	1 (0.7%)	1	0 (0.0)	0
Tendonitis	0 (0.0)	0	1 (2.0%)	1
Wrist fracture	0 (0.0)	0	1 (2.0%)	1
Skin and subcutaneous tissue disorders	**10 (6.9%)**	**15**	**2 (4.0%)**	**2**
Acne	1 (0.7%)	1	0 (0.0)	0
Actinic keratosis	1 (0.7%)	1	0 (0.0)	0
Dermatitis atopic	1 (0.7%)	1	0 (0.0)	0
Dermatitis contact	2 (1.4%)	2	0 (0.0)	0
Erythema	1 (0.7%)	1	0 (0.0)	0
Herpes Zoster	1 (0.7%)	1	0 (0.0)	0
Papule	1 (0.7%)	1	1 (2.0%)	1
Rash	2 (1.4%)	4	0 (0.0)	0
Seborrhoeic dermatitis	1 (0.7%)	1	0 (0.0)	0
Squamous cell carcinoma of skin	1 (0.7%)	1	0 (0.0)	0
Urticaria	1 (0.7%)	1	1 (2.0%)	1

* n=143 is based on 97 Subjects treated Bellafill from study Period I and 46 Period II Control subjects that crossed over and were treated with Bellafill

14 Bellafill and no Control subjects experienced Treatment-Related Adverse Events (TRAEs). Twelve (12) adverse events were mild, one (1) case of injection site reaction was moderate in severity, and one (1) injection site bruising was severe in intensity. Eleven (11) events resolved and three (3) cases of injection site reaction (lumpiness directly after injection) persisted throughout the study. Two (2) of these events were deemed by the investigator to be mild and one event was deemed to be of moderate severity. All TRAEs reported in Bellafill subjects by severity and duration are presented in Table 8 and 9, respectively.

Table 8. Summary of TRAE (by Severity)

System Organ		Subject (n=143)	Events

Class/Preferred Term			
Any TRAE		14 (9.8%)	14
	Mild	12 (8.4%)	12
	Moderate	1 (0.7%)	1
	Severe	1 (0.7%)	1
General disorders and administration site conditions			
Implant site mass		1 (0.7%)	1
	Mild	1 (0.7%)	1
	Moderate	0	0
	Severe	0	0
Injection site pain		3 (2.1%)	3
	Mild	3 (2.1%)	3
	Moderate	0	0
	Severe	0	0
Injection site reactions (i.e., lumpiness and papule formation)		4 (2.8%)	4
	Mild	3 (2.1%)	3
	Moderate	1 (0.7%)	1
	Severe	0	0
Swelling		1 (0.7%)	1
	Mild	1 (0.7%)	1
	Moderate	0	0
	Severe	0	0
Injection site bruising		3 (2.1%)	3
	Mild	2 (1.4%)	2
	Moderate	0	0
	Severe	1 (0.7%)	1
Tenderness		1 (0.7%)	1
	Mild	1 (0.7%)	1
	Moderate	0	0
	Severe	0	0
Skin and subcutaneous tissue disorders			
Acne		1 (0.7%)	1
	Mild	1 (0.7%)	1
	Moderate	0	0
	Severe	0	0

Table 9. Summary of TRAE (by Duration)

System Organ Class/Preferred Term		Subject (n=143)	Events
Any TRAE	N	14	14
	Mean No. days (SD)	30.8 (53.8)	
	Median (min, max)	16 (1, 180)	
General disorders and administration site conditions			

Implant site mass		1	1
	Mean No. days (SD)	180 (0)	
	Median (min, max)	180 (180, 180)	
Injection site pain		3	3
	Mean No. days (SD)	3.7 (1.5)	
	Median (min, max)	4 (2,5)	
Injection site reactions (i.e., lumpiness and papule formation)		4	4
	Mean No. days (SD)	76 (0)	
	Median (min, max)	76 (76, End of study)	
Swelling		1	1
	Mean No. days (SD)	1 (0)	
	Median (min, max)	1 (1,1)	
Injection site bruising		3	3
	Mean No. days (SD)	17.3 (0.6)	
	Median (min, max)	17 (14, 18)	
Tenderness		1	1
	Mean No. days (SD)	3 (0)	
	Median (min, max)	3 (3,3)	
Skin and subcutaneous tissue disorders			
Acne		1	1
	Mean No. days (SD)	16 (0)	
	Median (min, max)	(16, 16)	

Five serious adverse events (SAEs) were noted during the study; lower back nerve impingement (Bellafill patient), West Nile meningitis (Bellafill patient), exacerbation of depression (Bellafill patient), recurrence of breast cancer (Control subject), and cholecystitis (Control subject). None were deemed related to study treatment. There were no deaths during the study.

Adverse events of special interest were followed separately for the study. These included hyper and hypopigmentation, hypertrophic scarring or keloid formation and the appearance of granulomas. None of these adverse events were reported.

Subject Diary:
Subjects were asked to keep diary cards and grade symptoms of erythema, swelling, bruising, pain, itching, lumps/bumps and discoloration. Subjects' scores for the severity of these events after the initial treatment are presented in Table 10 and durations are provided in Table 11. Similar subject diary outcomes were noted following touch-up treatment injections.

Table 10. Maximum intensity of Signs/Symptoms after Initial Bellafill Treatment Per Patient as Obtained from Subject Diary (n=130)*****

Sign/symptom (R&L side combined)	**None N (%)**	**Mild N (%)**	**Moderate N (%)**	**Severe N (%)**
Any sign/symptom	14 (10.8%)	54 (41.5%)	51 (39.2%)	11 (8.5%)

Swelling	40 (30.8%)	48 (36.9%)	38 (29.2%)	4 (3.1%)
Erythema	44 (33.8%)	60 (46.2%)	23 (17.7%)	3 (2.3%)
Pain	47 (36.2%)	52 (40.0%)	28 (21.5%)	3 (2.3%)
Bruising	53 (40.8%)	49 (37.7%)	23 (17.7%)	5 (3.8%)
Lumps/bumps	55 (42.3%)	45 (34.6%)	27 (20.8%)	3 (2.3%)
Itching	97 (74.6%)	26 (20.0%)	7 (5.4%)	0 (0.0%)
Discoloration	102 (78.5%)	21 (16.2%)	6 (4.6%)	1 (0.8%)

***** Number of treated subjects returning diaries, combined for Period I and Period II data Percentages are based on the number of subjects returning diaries

Table 11. Duration of Signs/Symptoms after Initial Bellafill Treatment from Subject Diary (n=130)*

Sign/symptom (R&L side combined)	**Any**	**1 Day**	**2-7 Days**	**8-14 Days**
Any sign/symptom	116 (89.2%)	7 (5.4%)	61 (46.9%)	48 (36.9%)
Erythema	86 (66.2%)	34 (26.2%)	39 (30.0%)	13 (10.0%)
Swelling	90 (69.2%)	15 (11.5%)	65 (50.0%)	10 (7.7%)
Bruising	77 (59.2%)	7 (5.4%)	44 (33.8%)	26 (20.0%)
Pain	83 (63.8%)	17 (13.1%)	57 (43.8%)	9 (6.9%)
Itching	33 (25.4%)	10 (7.7%)	19 (14.6%)	4 (3.1%)
Lumps/bumps	75 (57.7%)	14 (10.8%)	44 (33.8%)	17 (13.1%)
Discoloration	28 (21.5%)	5 (3.8%)	13 (10.0%)	10 (7.7%)

* Number of treated subjects returning diaries, combined for Period I and Period II data Percentages are based on the number of subjects returning diaries

Subgroup Analyses

As illustrated in Table 12, subgroup comparisons of TRAEs in the initially randomized subjects displayed similar incidence rates for each pre-specified subgroup.

Table 12. Subgroup Analyses of Treatment-Related Adverse Events

Subgroup		**Bellafill** n=97	**Control** n=50
Gender	Male (n=37)	4 (10.8%)	0.0
	Female (n=60)	4 (6.7%)	0.0
Fitzpatrick Skin Type	I-IV (n=72	6 (8.3%)	0.0
	V-VI (n=25)	2 (8.0%)	0.0
Age	≤45 (n=49)	3 (6.1%)	0.0
	>45 (n=48)	5 (10.4%)	0.0

2. Effectiveness Results

Primary Effectiveness Endpoint:

The primary effectiveness was analyzed as a responder analysis, in which the criterion for success was defined as 50% or more of treated scars for a subject improved by two or more points on the ASRS at the 6 month visit (as evaluated by a live blinded evaluator). The observed

success rate at 6 months in the Bellafill group was 56/87 (64%) and significantly higher than in the Control group 15/46 (33%).

Secondary Effectiveness Endpoints Outcomes

The following additional effectiveness endpoints were evaluated.

- A secondary effectiveness endpoint was a responder analysis (i.e., success was defined as 50% or more of treated scars on a subject improved by two or more points) determined via validated 4-point ASRS at each time point by a live, Blinded Evaluator. The observed success rates in unblinded assessments at 9 and 12 months for the Bellafill group were 48/78 (61.5%) and 58/82 (70.7%). Table 13 presents the ASRS responder rates determined by the Blinded Evaluator at all time points.

Table 13 Mean Blinded ASRS Scores from Baseline through Month 12*

Time		**Bellafill** n=97	**Control** n=50
Baseline	n	97	50
	Mean ± SD	3.3 +/- 0.3	3.3 +/- 0.3
	Median (P25, P75)	3.2 (3.0, 3.4)	3.2 (3.0, 3.5)
Week 4	n	93	48
	Missing values	4	2
	Mean ± SD	2.2 +/- 0.7	2.4 +/- 0.7
	Median (P25, P75)	2.2 (1.8, 2.7)	2.4 (2.0, 2.9)
	Change from BL[+]	-1.1 (-1.2, -0.9)	-0.8 (-1.0, -0.7)
	Responder rate*	26.9 (18.2, 37.1)	18.8 (8.9, 32.6)
Week 6	n	75	42
	Missing values	22	8
	Mean ± SD	1.8 +/- 0.6	2.2 +/- 0.8
	Median (P25, P75)	1.6 (1.2, 2.2)	2.1 (1.5, 2.8)
	Change from BL	-1.5 (-1.7, -1.4)	-1.1 (-1.3, -0.8)
	Responder rate*	60.0 (48.0, 71.1)	33.3 (19.6, 49.5)
Week 8	n	81	44
	Missing values	16	6
	Mean ± SD	1.8 +/- 0.7	2.2 +/- 0.8
	Median (P25, P75)	1.5 (1.3, 2.1)	2.2 (1.5, 2.8)
	Change from BL	-1.5 (-1.7, -1.4)	-1.1 (-1.3, -0.8)
	Responder rate*	66.7 (55.3, 76.8)	40.9 (26.3, 56.8)
Month 3	n	85	42
	Missing values	12	8
	Mean ± SD	1.7 +/- 0.7	2.2 +/- 0.8
	Median (P25, P75)	1.5 (1.3, 2.2)	2.0 (1.4, 2.7)
	Change from BL	-1.5 (-1.7, -1.4)	-1.1 (-1.4, -0.9)
	Responder rate*	62.4 (51.2, 72.6)	35.7 (21.6, 52.0)
Month 6	n	87	46
	Missing values	10	4
	Mean ± SD	1.8 +/- 0.6	2.2 +/- 0.7
	Median (P25, P75)	1.6 (1.3, 2.3)	2.3 (1.6, 2.7)
	Change from BL	-1.5 (-1.6, -1.3)	-1.1 (-1.3, -0.9)
	Responder rate*	64.4 (53.4, 74.4)	32.6% (19.5%, 48.0%)
Month 9	n	78	
	Missing values	19	

	Mean ± SD Median (P25, P75) Change from BL Responder rate*	1.7 +/- 0.5 1.6 (1.3, 2.0) -1.7 (-1.7, -1.5) 61.5 (50.7, 72.3)	n/a
Month 12	n Missing values Mean ± SD Median (P25, P75) Change from BL Responder rate*	82 15 1.6 +/- 0.5 1.5 (1.2, 1.0) -1.7 (-1.8, -1.6) 70.7 (60.9, 80.6)	n/a

BL^{+} - Baseline

* Assessments at Months 9 and 12 were unmasked.

** Responder was defined as a greater than or equal to two-point improvement on the ASRS in more than 50% of a patient's treated scars

1. Wilcoxon Rank Sum test for Change from Baseline
2. Fisher Exact test for Responder Rate 95% CI

- Subject Assessment of Scar Correction (SASC) - At the Month 3 visit, the proportion of subjects judging themselves as "very satisfied", "satisfied" or "somewhat satisfied" on the 6 point SASC scale were 73/85 (85.9%) and 25/43 (58.1%) for Bellafill and Control patients, respectively. At the 6 Month visit, Bellafill and Control subjects were satisfied at a rate of 73/87 (83.9%) and 24/46 (52.2%), respectively. The proportion of unblinded subjects who reported being "very satisfied" or "satisfied" at month 9 was (83.3%) 65/78 and (90.4%) 75/83 at month 12.

- Subject Global Aesthetic Improvement Scale (SGAIS) - At the Month 3 visit, the proportion of subjects indicating their appearance was "Improved" or "Much Improved" on the five point SGAIS was 67/85 (78.8%) and 19/43 (44.2%) for Bellafill and Control subjects, respectively. At Month 6, the proportion of subjects was 67/87 (77.0%) and 19/46 (41.3%) for Bellafill and Control subjects, respectively. The proportion of unblinded subjects who reported their appearance as "Improved" or "Much Improved" was 84.6% (66/78) at Month 9 and 83.1% (69/83) at the Month 12 visit.

- Physician Global Aesthetic Improvement Scale (PGAIS) - The proportion of blinded evaluators indicating improvement (i.e., "Improved" or "Much Improved") as per the PGAIS scale at Month 6 was 83.9% and 54.3% in the Bellafill and control groups, respectively). The proportion of unblinded investigators indicating improvement at Month 9 and Month 12 were 94.9% and 97.6%, respectively

- Independent Masked Photographic Review (IPR) - An independent masked review was performed on the photographs from the 6 Month visit by board-certified physicians. The objective was to determine the extent of agreement with the live Blinded Evaluator assessments (i.e., Primary Effectiveness endpoint) and PGAIS assessment by the Blinded Evaluator. IPR analysis via the ASRS scale revealed a greater response rate for Bellafill than Control subjects (i.e., 6.9% and 0% respectively); however, these response rates were considerably lower than those determined by live Blinded Evaluators. Using the PGAIS scale, the IPR found that 63/87 (72/%) of the Bellafill subjects displayed a "Improved" or "Much Improved" response compared to 22/46 (48%) Control patients.

- Sensitivity Analyses – were performed to assess the potential impact of missing data on the primary effectiveness outcome. In these analyses missing values were examined using analyses where non-completers were considered as: a) failures, and b) successes. The results of these sensitivity analyses suggested that the difference between the two groups remained in favor of the Bellafill group.

- Learning curve - The existence of a "learning curve" was evaluated by comparing the ASRS responder rates at the 6 Month visit for the first versus the last 50% of treated subjects for both treatment groups. Responder rates were similar for all Bellafill subjects regardless of the timing of enrollment. In both strata, the Bellafill responder rate was superior to Control.

- Per scar analysis - in addition to assessing patient responder rates, the response rate of individual scars was determined. In this analysis, scars with a greater than or equal to a two - point improvement on the ASRS over baseline were considered responders, 442/789 (56.0%) of scars in the Bellafill group were successes compared to 118/397 (29.7%) of scars in the Control group. Bellafill injections were also superior to Control treatment at all study visits after the Week 4 touch-up injection.

3. Subgroup Analyses

Subgroup Analyses – As illustrated in Table 13, the Bellafill subjects performed better than Control patients in the Blinded Evaluator ASRS scores (at Month 6) for each pre-specified patient subgroup tested.

Table 13. ASRS Responder Rate in Various Subgroups at Month 6

Subgroup		**Bellafill** ***n=97***	**Control** ***n=50***
Gender	Female	60.0%	35.7%
	Male	71.9%	27.8%
Age Group	≤ 45	64.3%	27.3%
	> 45	64.4%	37.5%
Fitzpatrick Skin Type	I-IV	58.7%	32.4%
	V-VI	79.2%	33.3%
Number of treated scars	< 8	64.3%	38.1%
	≥ 8	64.4%	28.0%

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 10 investigators. 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.

X. *SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION*

- **Relevant Post Market Experience**

Since product approval for the correction of nasolabial folds, the adverse events received via Bellafill post-marketing surveillance in on-label or off-label settings were infrequent. Those events that were reported in five or more instances include (in order of decreasing frequency reported) lumps/bumps, swelling, nodules, bruising, granuloma, redness, and reported allergic reactions. Time to onset for these events ranged from immediate to three and a half years post-injection. The majority of the events, (when severity was reported) were mild in severity and no events were characterized as serious. Outcomes for these events ranged from resolution to ongoing at the time of last contact. The treatments for these events included massage**,** ice packs, warm compress**,** antibiotics**,** antihistamines, various energy treatments, oral and intralesional steroids, and device excision.

Adverse events possibly related to intravascular injection have been reported. Symptoms ranged from possible skin discoloration to bumps to skin necrosis. Time of onset, (when known), ranged from the day of injection to 3 days post treatment. The majority of the intravascular injection events were mild in severity and no events were reported as serious. Treatments included nitroglycerin paste, aspirin, and warm compresses. These events resolved or were resolving within one month after onset.

A single case of blindness was reported as a Medical Device Report (MDR) after Bellafill injection. The patient was injected in the right canthal area (periorbital), and experienced immediate onset of loss of vision in the right eye. Treatments included IV saline, direct pressure release in the anterior chamber of the eye and treatment in a hyperbaric oxygen chamber. The patient's vision did not return. In this patient case, periorbital injection of Bellafill was outside the recommended Indications for Use.

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

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

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Safety Conclusions

The adverse effects of the device are based on data collected in the Pivotal Study (SUN-11-001) to support PMA approval as described above as well as an evaluation of the Post Market Surveillance reports. The submitted data provided a reasonable assurance that the device is safe for correction of moderate to severe, atrophic, distensible facial acne scars on the cheek in patients over the age of 21 years. The specific conclusions are:

- Of the 175 subjects randomized in this study, 143 subjects received their first treatment with Bellafill at either the Day 0 or 6 Month visit. 46/143 (32%) of the Bellafill and 16/50 (32%) of the Control of subjects reported an all cause (i.e., related and unrelated causality) TEAE.

- 14 of the Bellafill and none of the Control subjects experienced a Treatment-Related AE (TRAE). The majority of TRAEs experienced by Bellafill subjects were mild in intensity (12/14). One case of injection site reaction was moderate in severity, and one injection site bruising was judged to be severe in intensity.

- The commonly reported TRAEs were: implant site mass, injection site pain, injection site reaction (i.e., lumpiness and papule formation), swelling, injection site bruising and tenderness. Eleven of these events resolved and three cases of injection site reaction (lumpiness directly after injection) persisted throughout the study. Two of these events were deemed by the investigator to be mild and one event was deemed to be of moderate severity.

- The incidence of TRAEs for all subgroups evaluated (i.e., male vs. female, skin types I-IV compared to V-VI and patients over and under the age of 45) were similar to the event rates for the general study population. Hence, no differences in safety profile were observed for any evaluated subgroup. In addition, there were no reports of hyper or hypopigmentation, hypertrophic scarring, keloid formation or the appearance of granulomas reported in the Pivotal Study.

- There were no deaths during the study. Five serious adverse events (SAEs) were noted during the study, i.e., cholecystitis, lower back nerve impingement, recurrence of breast cancer, West Nile meningitis and exacerbation of depression. None of the SAEs were deemed to be related to study treatment.

- Almost all (89%) of the subjects injected with Bellafill reported adverse signs and symptoms in a 14 day patient diary. The majority of these signs/symptoms were either mild (41.5%) or moderate (39.2%) in severity and the most common signs and symptoms reported were swelling, erythema, pain, bruising and lumps/bumps. The majority (63%) of these signs/symptoms resolved in less than 2 weeks.

- Review of the Post Marketing Surveillance database for off-label use of Bellafill in the correction of acne scars on the cheek revealed that product use in the commercial setting did not introduce any new or different types of safety concerns.

- Rare risks include vascular occlusion (including ocular) from embolization and infection. These were not observed in this pivotal study of 143 treated patients.

B. Effectiveness Conclusions

Assessment of product effectiveness is based on the results of Pivotal Study SUN-11-001. These submitted data provided a reasonable assurance that the device is effective for use in the

correction of moderate to severe, atrophic, distensible facial acne scars on the cheek in patients over the age of 21 years. The specific conclusions are:

- The trial was a well-designed prospective, controlled study using a validated scale and blinded, live evaluations. The data are considered to be as robust as possible for an aesthetic indication. The study met the pre-specified primary effectiveness criterion. The observed success rate at 6 months in the Bellafill group was 64% (56/87) and significantly higher than in the Control group 33% (15/46).

- The study met the pre-specified secondary effectiveness endpoints for correction of moderate to severe, atrophic, distensible facial acne scars on the cheek in patients older than 21 years of age. Specifically, the Blinded Evaluators' assessment of scar severity via ASRS ratings were superior for Bellafill subjects (compared to Control patients) at each time point after touch-up treatment was complete at Week 4 (i.e., Weeks 6 and 8 as well as Months 3 and 6.) The proportion of Blinded Evaluators indicating improvement (i.e., "Improved" or "Much Improved") on the PGAIS scale at 6 months was 83.9% and 54.3% for the Bellafill and Control groups, respectively. Regarding the duration of product effectiveness, 61.5% and 70.7% of the Bellafill subjects were judged responders at the 9 and 12 month visits, respectively, in an unmasked evaluation.

- Assessment at the 3 and 6 Month visits revealed that the subject assessment of scar correction (SASC) and the subject global aesthetic improvement scale (SGAIS) values were superior for Bellafill subjects when compared to Control patient outcomes. With the SASC, 84% of the Bellafill and 52.2% of the Control subjects were satisfied at the 6 month visit. Subject assessment via a GAIS indicated 77.0% of the Bellafill and 41.3% of the Control subjects showed improvement at the 6 month visit.

- A per scar analysis based on the live Blinded Evaluator assessment at Month 6 indicated that 442/789 (56.0%) of scars in the Bellafill group and 118/397 (29.7%) of scars in the Control group were responders (i.e., a scar that demonstrated at least a 2 grade improvement on the ASRS scale). The Bellafill scar responder rate was also superior to Control treatment at all study visits after completion of the Week 4 touch-up visit.

- Independent masked review of photographs (IPR) from the 6 Month visit by three board-certified physicians revealed a higher ASRS response rates for Bellafill than Control subjects, but the response rates were considerably lower than those determined by live Blinded Evaluators. PGAIS scale assessment by the IPR found that a greater number of Bellafill patients graded "Improved" or "Much Improved" when compared to Control patients.

- Subgroup Analyses for gender, age, Fitzpatrick Skin Type and number of scars treated (based on the Blinded Evaluator ASRS scores at the Month 6 visit) found that the Bellafill patients displayed better outcomes than Control subjects in all pre-specified patient subgroups.

C. Benefit-Risk Conclusions

The benefits as determined by the improvement seen on the Acne Scar Rating Scale and patient satisfaction and the risks as assessed from short term adverse outcomes and rare late adverse events seen after injection, are sufficiently well understood for patients to make informed decisions about device use.

In conclusion, given the available information above, the data support that for correction of nasolabial folds and moderate to severe, atrophic, distensible facial acne scars on the cheek in patients over the age of 21 years 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.

XIII. CDRH DECISION

CDRH issued an approval order on December 23, 2014.

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