Bellafill®

Instructions for Use

Caution: Federal Law restricts this device to sale by or on the order of a physician or licensed practitioner.

DESCRIPTION

Bellafill[1] is an implant composed of non-resorbable polymethylmethacrylate (PMMA) microspheres, 30 to 50 microns in diameter, suspended in a water based carrier gel composed 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.

INTENDED USE / INDICATIONS

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.

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.

[1] Bellafill® formerly known as ArteFill®

WARNINGS

- The safety of Bellafill when used within 6 months of collagen, botulinum toxin, or other wrinkle therapies has not been studied.
- A Bellafill Skin Test must be administered and evaluated prior to injection of Bellafill. Patients demonstrating a positive skin test or 2 equivocal skin tests should not be considered candidates for treatment. Patients demonstrating an anti-bovine collagen serum IgG level outside of the normal range at baseline also should not be considered candidates for treatment. Refer to the Bellafill Skin Test Instructions for Use.
- Use of Bellafill at specific sites in which an active inflammatory process (skin eruptions such as cysts, pimples rashes, or hives) or infection is present should be deferred until the inflammatory process has been controlled.
- Bellafill must not be implanted into blood vessels. Localized superficial necrosis and scarring may occur after injection in or near blood vessels, such as in the lips, nose, or glabellar area. It is thought to result from the injury, obstruction, or compromise of blood vessels.
- As with all dermal filler procedures, Bellafill should not be used in vascular rich areas. Use of similar products in these areas, such as glabella and nose, has resulted in cases of vascular embolization and symptoms consistent with ocular vessel occlusion, such as blindness. For additional information please see the Post-Marketing Surveillance Section in Adverse Events.

PRECAUTIONS

- Bellafill contains non-absorbable PMMA microspheres. Implantation is permanent and will not be reversed without physical removal.
- The safety of Bellafill for use during pregnancy and in breastfeeding females has not been established.
- Bellafill is packaged in a sealed tray containing individual treatment syringes with sterile needles for single patient use, packaged in a box. The tip of the syringe is sealed with a tamper evidence cover. Do not use if the seal on the tray lid or syringe is broken or removed. Do Not Resterilize.
- The safety of injecting greater amounts than 3.5 cc per treatment site or 8.9 cc overall has not been established.
- The safety and effectiveness of Bellafill for the treatment of non-distensible atrophic acne scars has not been established. The use of Bellafill for ice pick or sinus tract scars has not been studied.
- The safety and efficacy of Bellafill for nasolabial fold wrinkles and cheek acne scars have not been established in patients under the age of 21 years. There is limited information on the safety of Bellafill in patients less than 36 years of age. In the pivotal Acne Scar study of Bellafill, the incidence of injection site reactions in subjects less than 36 years old (30 subjects) was similar to the incidence in subjects above the age of 36 (113 subjects). The majority of these injection site reactions were mild in severity.
- The safety in patients with known susceptibility to hyperpigmentation, keloid formation and hypertrophic scarring has not been studied. Formation of hyperpigmentation, keloids or

hypertrophic scars may occur after dermal filler injections including Bellafill. In the pivotal Acne Scar study of Bellafill, the incidence and severity of adverse events in 34 subjects with Fitzpatrick Skin Types V and VI was similar to that reported in 109 patients with Fitzpatrick Skin types I - IV and no unique adverse events associated with these patient subgroups were observed.

- As with all transcutaneous procedures, Bellafill injection carries a risk of infection. The usual precautions associated with injectable materials should be followed.
- The safety of Bellafill in patients on immunosuppressive therapy has not been established.
- The safety of Bellafill in patients with connective tissue disorder has not been established.
- Bruising or bleeding may occur at Bellafill injection sites. Use of Bellafill in patients who have undergone therapy with thrombolytics, anticoagulants, or inhibitors of platelet aggregation within 3 weeks preceding treatment has not been studied.
- Patients should minimize exposure of the treated area to excessive sun, UV lamp exposure and extreme cold weather at least until any initial swelling and redness has resolved.
- If laser treatment, chemical peeling or any other procedure based on active dermal response is considered after treatment with Bellafill, there is a possible risk of eliciting an inflammatory reaction at the implant site. This also applies if Bellafill is administered before the skin has healed completely after such a procedure.
- The use of Bellafill in anatomical spaces other than the dermis for correction of nasolabial folds and for acne scars on the cheek has not been studied . Refer to the clinical studies section for more information on implantation sites that have been studied.
- The use of Bellafill in patients with thin or flaccid skin has not been studied and the cosmetic results for these patients are unknown.
- Long-term safety and effectiveness of Bellafill beyond one year has not been established.
- After use, treatment syringes and needles may be potential biohazards. Handle accordingly and dispose of in accordance with accepted medical practice and applicable local, state, and federal requirements.
- Bellafill has an opaque, off-white appearance. In the event that the content of a syringe shows signs of separation and/or appears clear (like water), do not use the syringe and notify Suneva Medical immediately. In the United States or Canada, call toll free (888-278-3345). Outside the United States or Canada, call ++1-858-550-9999.
- Bellafill should not be mixed with other products before implantation of the device.

ADVERSE EVENTS

a) U.S. Controlled Nasolabial Fold (NLF) Clinical Trial

All adverse events (AEs), including those attributed and not attributed to treatment, reported in Bellafill or Control subjects at an incidence of 1% or greater in U.S. studies are presented in **Table 1** below in descending order according to frequency in the Bellafill group.

Table 1. Adverse Events Reported at an Incidence of 1% or Greater in U.S. NASOLABIAL fold clinical trials of Bellafill

Event	Number of Events (Events/subjects treated, %)		
	Bellafill[1] n = 285	Bellafill[2] n = 106	Control[3, 4] n = 123
Lumpiness at injection area more than one month after injection	13 (4.6)		4 (3.3)
Persistent swelling or redness	10 (3.5)	3 (2.8)	13 (10.6)
Increased sensitivity	5 (1.8)	2 (1.9)	
Rash, itching more than 48 hours after injection	4 (1.4)		2 (1.6)
Sensitization reactions			6 (4.9)
Abscess			3 (2.4)
Visibility of puncture area			2 (1.6)

[1] 128 Bellafill subjects in the controlled study and 157 subjects in an open label study, who were followed for 1 year after implantation.

[2] 106 Control subjects who received Bellafill in the cross-over arm of the controlled study and were followed for 6 months after implantation.

[3] 123 subjects who received the Control treatment in the controlled study and were followed for 6 months after implantation.

[4] The Control treatment in study was a commercially available collagen implant (Zyplast®).

No systemic adverse events were reported at an incidence of 1% or greater. One severe adverse event (granuloma or enlargement of the implant) and 14 moderate adverse events (persistent swelling or redness, lumpiness at injection site more than 1 month after injection, blurred vision, flu-like symptoms, abscess, granuloma or enlargement of the implant, alopecia areata) were reported for Bellafill subjects. Nine severe adverse events (lumpiness at injection site more than 1 month after injection, abscess, infection, granuloma or enlargement of the implant, sensitization reactions, increased sensitivity, persistent swelling or redness), and 12 moderate adverse events (persistent swelling or redness, rash, itching more than 48 hours after injection, sensitization reactions, lumpiness at injection site more than 1 month after injection, visibility of the puncture area, abscess) were reported for Control subjects.

Local adverse events reported in Bellafill subjects at an incidence of less than 1% in US studies, whether or not they were determined to be related to the implant, were sensitization reactions, abscess, visibility of the puncture area, blurred vision, flu-like symptoms, recurrence of existing herpes labialis, granuloma or enlargement of the implant, acneiform lesions, occasional tenderness, redness and visible capillaries, alopecia areata, and dry skin. Systemic adverse events reported at an incidence of less than 1% were mild chest congestion and fainting. One subject was diagnosed with breast cancer, determined by the investigator not to be related to the implant.

For Control subjects, local adverse events reported at an incidence of less than 1%, whether or not they were determined to be related to the implant, were increased sensitivity, flu-like symptoms, granuloma or enlargement of the implant, infection, and acneiform reaction. One subject died of trauma unrelated to the implant.

Adverse Events Lasting Longer Than Two Weeks

The following is a summary of the reported duration of adverse events lasting longer than 2 weeks in Bellafill subjects (n=391 subjects) in US studies: lumpiness at injection site more than 1 month after injection (n=12 events), duration varied from 4 weeks to unresolved at 26 weeks; persistent swelling or redness (n=8 events), duration varied from 5 weeks to unresolved at 26 weeks; increased sensitivity (n=7 events), duration varied from 4 weeks to unresolved at 26 weeks; rash and itching (n=2 events), duration varied from 3 weeks to 6 weeks; sensitization reactions (n=2 events), duration varied from 19 weeks to unresolved at 26 weeks; visibility of the puncture site (n=1 event), duration was 13 weeks; granuloma or enlargement of the implant (n=4 events), duration varied from 10 weeks to unresolved at 26 weeks; other local complications (n=5 events), duration was unresolved at 26 weeks. One subject suffered from breast cancer unrelated to the implant.

Reported duration of adverse events lasting longer than 2 weeks in Control subjects (n=123 subjects): lumpiness at injection site more than 1 month after injection (n=2 events), duration varied from 13 weeks to unresolved at 26 weeks; persistent swelling or redness (n=12 events), duration varied from 7 weeks to unresolved at 26 weeks; increased sensitivity (n=1 event), duration was unresolved at 26 weeks; rash and itching (n=2 events), duration was unresolved at 26 weeks; sensitization reactions (n=4 events), duration varied from 7 weeks to unresolved at 26 weeks; abscess (n=2 events), durations were unresolved at 26 weeks; visibility of the puncture site (n=1 event), duration was unresolved at 26 weeks; granuloma or enlargement of the implant (n=1 event), duration was unresolved at 26 weeks; flu-like symptoms (n=1 event), duration was unresolved at 26 weeks. One subject died from an accident unrelated to the implant.

Adverse Events Reported Three Months or Longer after Treatment

Among the 391 subjects treated with Bellafill, adverse events with reported onset dates 3 months or more after treatment were lumpiness at the injection site (6), rash and itching (3), sensitization reaction (2), increased sensitivity (2), persistent swelling and redness (1), granuloma or granulomatous inflammation (1), alopecia areata (1), visibility of the puncture site (1), and redness and visible capillaries near the area of injection (1).

Among the 123 Control subjects, adverse events with reported onset dates 3 months or more after treatment were abscess (1), infection (1), lumpiness (1), acneiform reaction (1), flu-like symptoms (1), persistent swelling or redness (1), and trauma fatality not related to the implant (1).

b) U.S. Controlled Acne Scar Clinical Trial

The U.S. Acne Scar pivotal study (Study SUN-11-001) involved 147 treated subjects at 10 centers. At baseline, subjects were randomized to receive Bellafill in the cheeks or Saline (Control group). At 6 months, all Control subjects were eligible to receive treatment with Bellafill.

Of the 147 subjects treated in the study, 143 subjects received a treatment with Bellafill at either baseline/Day 0 (Period I) or at Month 6 (Period II, Track B). Therefore the safety information reflects 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 were initially enrolled in the control treatment arm.

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 initial treatment are presented in **Table 2** and durations are provided in **Table 3**, respectively. Subjects who observed any signs or symptoms (89.2%), experienced them shortly after Bellafill treatment and the majority were mild to moderate in intensity. Subjects typically reported these diary card symptoms as resolved in 1-7 days. Similar subject diary outcomes were noted following touch-up treatment injections.

Table 2: Maximum intensity of Signs/Symptoms after Initial Bellafill Treatment 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%)

***** # treated subjects returning diaries, combined for Period I and Period II data

Percentages are based on the number of subjects returning diaries

Table 3: Duration of Signs/Symptoms after Initial Bellafill Treatment from Subject Diary (n=130)*

Sign/symptom (R&L side combined)	Any	1day	2-7days	8-14days
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%)

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

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 4

Table 4. 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

Five serious adverse events (SAEs) were noted during the study; cholecystitis, lower back nerve impingement, recurrence of breast cancer, West Nile meningitis and exacerbation of depression. 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.

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 treatment- related adverse events (TRAEs) reported in Bellafill subjects by severity and duration are presented in **Tables 5** and **6**, respectively.

Table 5: Summary of TRAE (by Severity)

System Organ Class/Preferred Term		Subject (n=143)	Events
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 6: Summary of TRAE (by Duration)

SOC/PT		Subject (n=143)	Events
Any TRAE	**n**	**14**	**14**
	Mean # days (SD)	30.8 (53.8)	
	Median (min.max)	16 (1,180)	
General disorders and administration site conditions			

Implant site mass	**n**	**1**	**1**
	Mean # days (SD)	180 (0)	
	Median (min.max)	180 (180,180)	
Injection site pain	**n**	**3**	**3**
	Mean # days (SD)	3.7 (1.5)	
	Median (min.max)	4 (2,5)	
Injection site reactions (i.e., lumpiness and papule formation)	**n**	**4***	**4**
	Mean # days (SD)	76 (0)	
	Median (min.max)	76 (76,76)	
Swelling	**n**	**1**	**1**
	Mean # days (SD)	1 (0)	
	Median (min.max)	1 (1,1)	
Injection site bruising	**n**	**3**	**3**
	Mean # days (SD)	17.3 (0.6)	
	Median (min.max)	17 (17,18)	
Tenderness	**n**	**1**	**1**
	Mean # days (SD)	3 (0)	
	Median (min.max)	3 (3,3)	
Skin and subcutaneous tissue disorders			
Acne	**n**	**1**	**1**
	Mean # days (SD)	16 (0)	
	Median (min.max)	16 (16,16)	

* Data doesn't include 3 subjects each with 1 unresolved event

POST-MARKETING SURVEILLANCE

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 (see Warnings section).

Adverse reactions should be reported to Suneva Medical, Inc. at 1-858-550-9999.

U.S. CLINICAL TRIALS

a) CONTROLLED NASOLABIAL FOLD TRIAL

A prospective, multi-center, double-masked, randomized trial compared Bellafill and a commercially available collagen implant for the treatment of soft tissue defects of the face. A total of 251 (i.e., 128 Bellafill and 123 Control) subjects were enrolled and the nasolabial folds of 212 (i.e., 108 Bellafill and 104 Control) subjects were treated.

The primary effectiveness endpoint was a comparison of the cosmetic correction provided by Bellafill and Control treatments at the end of a 6 month period after injection, evaluated by means of a validated facial fold assessment scale (FFA Scale) using standardized photographs as reference.
The numerical values for FFA Scale were: zero – no folds; one – folds just perceptible (i.e., ~0.1 mm); two – shallow folds with some defined edges (i.e., ~0.2 mm); three – moderately deep folds with some well-defined edges (i.e., ~0.5 mm); four – deep folds with most edges well-defined and some redundant folds (i.e., ~1.0 mm) and five – very deep folds with most edges well-defined and some redundant folds (i.e., ~2.0 mm). Comparisons to the reference photos were made at pre-treatment and at each follow-up visit. Safety was evaluated by comparing the incidence and severity of clinical events during and for 12 months after treatment completion.

Subject and Baseline Characteristics are presented in **Table 7**.

Table 7: Subject and Baseline Characteristics

Demographic	Bellafill (n = 128)	Control (n = 123)
Gender		
Male	11 (8.6%)	11 (8.9%)
Female	117 (91.4%)	112 (91.1%)
Age, years		
Mean	53.2	51.2
Range	28-82	29-78
Ethnicity		
Caucasian	100 (78.1%)	101 (82.1%)
Hispanic	21 (16.4%)	20 (16.3%)
Asian	1 (0.8%)	1 (0.8%)
Other[1]	6 (4.7%)	1 (0.8%)
Facial Area Treated		
Nasolabial Folds	108 (84.4%)	104 (84.6%)
Wrinkle Severity	**Mean Value**	**Mean Value**
Nasolabial Folds[2]	1.74	1.45

1. "Other" ethnicities, as reported by Bellafill subjects, were Mexican/Greek/English, Italian, Hispanic/Irish, American Indian, Native American, Middle Eastern. "Other" ethnicity, as reported by a Control subject, was Persian.
2. Subjects in the Bellafill treated group had a higher baseline fold severity than those in the Control group. The difference was statistically significant (p=0.039).

Results

The mean improvement in nasolabial fold wrinkle severity, as characterized by the masked observers, for subjects from before treatment to 6 months after completion of treatment was Bellafill - 0.77 points, and Control - 0.00 points. The difference was statistically significant (p = < 0.001).

Additional Analysis

At 1 month after treatment, 0.75 points (Bellafill) and 0.74 points (Control) differences from baseline for nasolabial fold wrinkle severity were recorded. At 3 months after treatment, differences of 0.81 points (Bellafill) and 0.15 points (Control) were determined for nasolabial folds. At 12 months after treatment, a nasolabial wrinkle severity difference of 0.98 points (compared to baseline) was recorded for Bellafill subjects. No assessment of nasolabial fold wrinkle severity was performed at 12 months after treatment for Control subjects.

The number of treatment sessions and volumes administered in nasolabial folds over the course of the study are displayed in **Table 8** and **9**, respectively.

Table 8: Mean Number of Treatment Sessions per Product

Area	Bellafill	Control
Nasolabial Folds	2.28 (n=108)	2.18 (n= 104)

Table 9: Mean Volume of Product used per Side (Left/Right)

Treatment Area	Bellafill (cc)	Control (cc)
Nasolabial Folds	0.82 (n=108)	1.46 (n= 104)

b) OPEN LABEL NASOLABIAL FOLD STUDY

This open-label, single-arm, multi-center study assessed the safety of Bellafill injections for the correction of soft tissue defects of the face. 157 subjects were enrolled and monitored at 3, 6, and 12 months post-treatment. 126/157 (80.2%) subjects completed the 1-year study. The safety data collected in this study were included in **Table 1**.

c) CONTROLLED ACNE SCAR STUDY

A prospective, multi-center, randomized, double-blind, controlled trial assessing the efficacy and safety of Bellafill for the correction of facial atrophic acne scars was conducted. A total of 147 (97 Bellafill and 50 Saline Control) subjects were enrolled and treated in the controlled phase of the study.

The primary effectiveness endpoint was a responder analysis in which the criteria for success at 6 months was defined as 50% or more of treated scars improving by 2 or more points, based on the blinded investigator assessment utilizing the validated 4-point Acne Scar Rating Scale (ASRS). The objective was to show that Bellafill was superior to Control in treating acne scars. The ASRS **(Table 10)** is a four point, static scale ranging from minimal to severe that relies on the depth of individual scars for severity assessment.

Table 10. 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

Subject and Baseline Characteristics are presented in **Table 11.**

Table 11. Subject and Baseline Characteristics

Demographic	Bellafill (n = 97)	Control (n = 50)
Gender		
Male	37 (38.1%)	20 (40.0%)
Female	60 (61.9%)	30 (60.0%)
Age, years		
Mean	44.6	45.3
Range	21-67	22-63
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		
Non-Hispanic	77 (79.4%)	37 (74.0%)
Hispanic	20 (20.6%)	13 (26.0%)

The number and severity of scars per subject are shown in **Table 12**. There were no differences between treatment groups regarding the number of qualifying scars or their severity. The median number of scars to be treated for each subject was 8.0 in each group with a median Acne Scar Rating Scale (ASRS) severity of 3.2 in each group.

Table 12: Acne Scar Characteristics at Baseline

Number and Severity of Scars		Bellafill (n = 97)	Control (n = 50)
Number of qualified scars/subject	N	97	50
	Mean ± SD	8.9 ± 4.6	8.5 ± 3.7
Mean scar severity	N	97	50
	Mean ± SD	3.3 ± 0.3	3.3 ± 0.3
Average volume/subject (mL) –Total	N	97	50
	Mean ± SD	1.50 ± 1.03	2.61 ± 1.80

Note: Mean ± standard deviation.

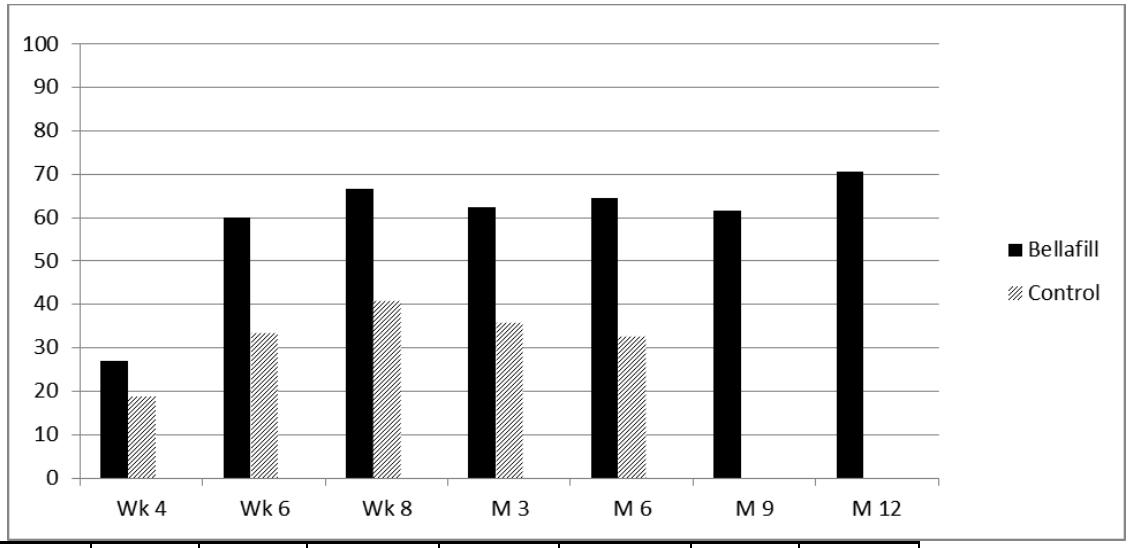
Results

The primary effectiveness endpoint was analyzed as a responder analysis, in which the criterion for success was defined as 50% or more of treated scars on a patient 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 (p=0.0005) than in the Control group 15/46 (33%).

Bellafill was found to be effective in all Fitzpatrick skin types, and for male subjects as well as female subjects.

A secondary effectiveness endpoint was a responder analysis (i.e., success was defined as 50% or more of treated scars on a patient improved by two or more points) determined via 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%). See **Figure 1**.

Figure 1: Proportion (%) of Responders Assessed by the Blinded Evaluator Based on the Observed Estimate



Bellafill Treatment	26.9%	60.0%	66.7%	62.4%	64.4%	61.5%	70.7%
Control Treatment	18.8%	33.3%	40.9%	35.7%	32.6%	NA	NA

Bellafill Responders / number of Subjects	25/93	60/75	54/81	53/85	56/87	48/78	58/82
Control Responders / number of Subjects	9/48	14/42	18/44	15/42	15/46	NA	NA

Additional Efficacy Analyses

In addition to assessing patient responder rates, the response rate of individual scars was also compared. In this analysis where 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 and 118/397 (29.7%) of scars in the Control group were judged as successes. Bellafill injections were superior to Control treatment at all study visits after the Week 4 touch-up injection.

Independent masked review of photographs (IPR) from the 6 Month visit by three board-certified physicians revealed a higher ASRS response rate for Bellafill than Control subjects, but these rates were lower than those determined by live Blinded Evaluators.

Subjects blinded to the treatment rated the overall degree of improvement in their treated scars using a five point, non-validated Subject Global Aesthetic Improvement Scale (SGAIS) where 5 was "much improved", 3 was "no change" and 1 was "much worse." Seventy-seven percent (77.0%) of subjects (67/87) treated with Bellafill and forty-one percent (41.3%) treated with Control (19/46) reported improvement in their global appearance at 6 months after their injection. Subjects who were treated with Bellafill continued to report improvement in their global appearance in an unblinded assessment at month 9 (84.6%) 66/78 and at month 12 (83.1%) 69/83.

BENEFIT / RISK CONCLUSIONS

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

d) COLLAGEN IMMUNOREACTIVITY

All subjects were required to have a skin test prior to being considered for injection with Bellafill.

Results of the skin tests – In the randomized NLF study, there were no positive skin tests in the 128 patients first randomized to receive Bellafill treatment or the 106 Control subjects who elected to receive Bellafill injections in the cross-over cohort. Of the 141 subjects who received the collagen Control skin test, 6 had a positive skin test and were excluded from the study.

Serum IgG – In the randomized NLF study, 4 Bellafill and 2 Control subjects were not treated because they displayed abnormal baseline serum IgG levels against collagen during screening. One subject in the Bellafill group transitioned from a normal IgG level before administration of the skin test to a value above the normal range at 1 month after treatment. This subject's IgG levels returned to the normal range by 3 months after treatment.

Acne Scar Study: 175 subjects received the Bellafill skin test. Three subjects (1.7%) demonstrated a positive skin test, and were excluded.

INDIVIDUALIZATION OF TREATMENT

A complete medical history should be obtained to determine whether the patient is an appropriate candidate for treatment with Bellafill.

HOW SUPPLIED

Bellafill is an aseptic product that is required to pass a USP sterility test before release. It is supplied in a sealed tray containing individual treatment syringes with sterile needles for single patient use, packaged in a box. Each syringe contains: 20% polymethylmethacrylate microspheres and 80% bovine collagen solution containing 3.5% bovine collagen, 2.7%

phosphate buffer, 0.9% sodium chloride, 0.3% lidocaine hydrochloride, and 92.6% water for injection.

The tray lid and tip of each individual syringe is sealed with a tamper evidence cover. Do not use if the tamper evidence cover is broken or removed. Do Not Sterilize.

IMMUNOGENICITY TEST PROCEDURE

Four (4) weeks prior to treatment, patients will be given a 0.1cc test injection of Bellafill skin test material intradermally in the volar forearm, to determine a patient's sensitivity to the treatment material. For a complete discussion of the Bellafill Skin Test, refer to the Instructions for Use supplied with test syringes.

Test Interpretation

The patient should observe the test site daily during the 4-week test period and notify the physician immediately if any effects indicative of a positive or equivocal response are observed or if systemic effects are experienced. A Bellafill Skin Test Results Card should be provided to the patient at the time of the skin test to help the patient assess the test site.

Positive Response

A positive response consists of erythema of any degree, induration, tenderness, and swelling, with or without pruritus, which can appear immediately following implantation and persists for more than 24 hours or appears more than 24 hours following implantation for any length of time.

Equivocal Response

An equivocal response is one in which there is no localized skin reaction, but the patient does elicit a possible systemic reaction such as a rash, arthralgia (aching joints), or myalgia (aching muscles) that occurs at any time during the 4-week observation period. If an equivocal response is observed, a second injection in the opposite arm is required, with observation for an additional 4 weeks. Patients demonstrating a positive or equivocal response in this second test should not be treated.

DIRECTIONS 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.

1. Prior to treatment with Bellafill, the results of the skin test must be carefully evaluated; the patient must not have a response to the required Bellafill Skin Test. For a complete discussion of the Bellafill Skin Test, refer to the Instructions for Use supplied with skin test syringes.
2. Prior to treatment with Bellafill, the patient should be fully informed of the indications, contraindications, warnings, precautions, treatment responses, adverse reactions, and method of administration. Patients also should be advised that supplemental touch-up treatments might be required to achieve correction.
3. A complete medical history should be obtained to determine whether the patient is an appropriate candidate for treatment with Bellafill.

4. The patient's soft tissue contour deficiencies should be characterized with regard to etiology, distensibility, and depth of lesion. Pretreatment photographs are recommended.
5. Scars selected for treatment should be atrophic distensible scars.
6. The Bellafill syringe must be brought to room temperature before injection.
7. After ensuring that the patient has thoroughly washed the treatment area with soap and water, the area should be cleaned with alcohol or other antiseptic.
8. Bellafill is implanted through a 26 G needle. Best results with Bellafill are achieved in defects requiring deep dermal implant placement and not into the subcutaneous fat. The rate and degree of correction in the implanted area varies with patient, treatment site, and plane of implant placement. Correction should be conservative during initial treatment.
9. Before injecting the patient, depress the syringe plunger until Bellafill is visible at the tip of the needle.
10. The best cosmetic result for NLFs can be achieved by a standard linear threading technique moving the needle back and forth beneath the skin being treated, maintaining constant injection pressure while withdrawing the needle (retrograde liner threading). Injection for acne scar can use both the retrograde linear threading and serial puncture techniques. The injection pressure is correct if the implant flows slowly and evenly, without great exertion. This technique forms a support structure beneath the skin to prevent further wrinkling and/or to maintain the scar correction.
11. If needles become occluded or dull during a treatment session, replacement may be necessary.
12. Gentle massage of the skin with the fingertips may facilitate even distribution of Bellafill immediately after implant placement.
13. The area and the borders of Bellafill injection should be recorded on an illustration of a face for later comparison
14. The physician should instruct the patient to report to him or her any evidence of adverse texture change in the surrounding treatment site. Other problems possibly associated with the use of Bellafill should be promptly brought to the attention of the physician
15. The syringe and any unused material should be discarded after a single treatment visit.
16. Correction should be limited to no more than 100% of the skin defect during treatment. One or two touch-up implantations at intervals of at least 2 weeks may be required to achieve the desired effect. The interval at which touch-up implantations are needed depends on the nature of the defect, the amount of implant injected, the site of placement, and the dynamics at the corrected sites.

STORAGE DIRECTIONS

Bellafill should be stored at standard domestic refrigerator temperatures. **DO NOT FREEZE**.

Bellafill has an off-white appearance. In the event that the content of a syringe shows signs of separation and/or is clear (like water), do not use the syringe and notify Suneva Medical immediately. In the United States or Canada, call toll-free 888-278-3345. Outside the United States or Canada call +1-858-550-9999.

PATIENT COUNSELING

Patients considering treatment with Bellafill should be provided with the patient labeling which is available by contacting Suneva Medical. Patients should be told that more than one treatment session might be required to achieve the desired correction.

ORDERING

To place an order, contact Suneva Medical, Inc. In the United States or Canada call toll-free 888-278-3345. Outside the United States or Canada call ++1-858-550-9999. Orders may also be sent by fax to 858-550-9997 or email to orders@sunevamedical.com.

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