

**BELLAFILL<sup>®</sup>**  
**PATIENT LABELLING**

**Table of Contents**

<b>1. GLOSSARY.....</b>	<b>2</b>
<b>2. PRODUCT DESCRIPTION – ABOUT BELLAFILL.....</b>	<b>4</b>
<b>3. INDICATION/INTENDED USE.....</b>	<b>4</b>
<b>4. SAFETY.....</b>	<b>4</b>
<b>5. RISKS.....</b>	<b>6</b>
<b>5. POST MARKETING SURVELLIANCE.....</b>	<b>7</b>
<b>6. ABOUT THE PROCEDURE.....</b>	<b>8</b>
<b>7. TROUBLESHOOTING:.....</b>	<b>9</b>
<b>8. CLINICAL STUDIES:.....</b>	<b>9</b>
<b>9. USER ASSISTANCE INFORMATION.....</b>	<b>12</b>

# 1. GLOSSARY

**ANAPHYLAXIS OR ANAPHYLACTIC SHOCK** — A sudden, severe and maybe fatal allergic reaction to a particular substance marked by a drop in blood pressure, itching, swelling and difficulty in breathing.

**ANESTHETIC** — A substance that reduces sensitivity to pain.

**ANTIBODIES** — An antibody (Ab) is a protein produced by plasma cells that is used by the immune system to identify and neutralize foreign objects such as bacteria and viruses.

**ATROPHIC** — A pit or depression of the skin.

**BOVINE COLLAGEN** — Collagen sourced from cows (see collagen).

**COLLAGEN** — A protein that provides the structural support for skin.

**CONTRAINDICATED** — Something that makes a particular treatment not safe to consider.

**CORTICOSTEROIDS** — Medication often used to treat swelling and redness (inflammation).

**DESENSITIZATION** — Medical therapy to make someone less sensitive to a specific substance (allergen) by adding amounts slowly over time to build up resistance.

**DISTENSIBLE** — Skin that looks smooth when stretched.

**ERYTHEMA** — Redness of the skin or mucous membranes, caused by any skin injury, infection, or inflammation.

**GRANULOMA** — A delayed reaction after injection of any dermal filler that may appear as a swollen lump but has a specific appearance when biopsied and viewed under a microscope.

**HYPERBARIC OXYGEN CHAMBER** — Oxygen therapy involves breathing pure oxygen in a pressurized room.

**HYPERPIGMENTATION** — A type of skin darkening that occurs when certain skin cells release more pigment (dark color).

**HYPERTROPHIC** — Thickened scarring within the boundaries of the initial wound.

**HYPOPIGMENTATION** — A loss of skin color, that occurs when certain skin cells do not release pigment to for skin color and sometimes results in patches of white skin.

**ICE PICK SCARS** — Scars with deep puncture-like marks.

**KELOID** — Irregular shaped scar that progressively enlarges and grows beyond the boundaries of the initial wound.

**LIDOCAINE** — A synthetic compound used as a local anesthetic (see anesthetic) to decrease pain.

**NASOLABIAL FOLDS** — Known as “smile lines”. They are the two skin folds that run from each side of the nose to the corners of the mouth.

**NSAIDS** — Non-steroidal anti-inflammatory drugs.

**IMMUNOSUPPRESSIVE THERAPY** — Medications commonly prescribed for those who have undergone an organ transplant, have cancer, or have auto-immune disorders such as rheumatoid arthritis, psoriasis, or inflammatory bowel disease.

**INJECTABLE** — Able to be injected with a needle or cannula.

**PMMA (POLY METHYLMETHACRYLATE)** — A non-degradable inert material used for various medical purposes over the last century.

**PMMA MICROSPHERES** — The tiny round and smooth particles made of PMMA, a plastic similar to Plexiglas that is commonly used in making contact lenses.

**SINUS TRACT SCARS** — Two scars that are connected by a hole extending between them.

## 2. PRODUCT DESCRIPTION – ABOUT BELLAFILL

### Q: WHAT IS BELLAFILL?

A: Bellafill is an injectable **bovine collagen** (sourced from calf) dermal filler with non-resorbable polymethylmethacrylate (**PMMA**) **microspheres** that provide structural support to the skin. It also contains 0.3% of local anesthetic (**lidocaine**). The lidocaine in Bellafill helps to improve the comfort of the injection.

### Q: HOW DOES BELLAFILL WORK?

A: Bellafill is a dual-acting injectable dermal filler. First, the **collagen** gel in Bellafill provides immediate volume and lift to correct the wrinkle and/or acne scar. The **PMMA microspheres** remain in place and create a base that provides structural support to the skin.

### Q: IS A SKIN TEST NECESSARY PRIOR TO TREATMENT WITH BELLAFILL?

A: A Bellafill Skin Test must be administered and evaluated prior to injection of Bellafill. Patients demonstrating a positive skin test or 2 skin tests with no local skin reactions but some systemic reactions should not be considered candidates for treatment. Patients demonstrating **antibodies** to **bovine collagen** outside of the normal range at baseline also should not be considered candidates for treatment. Refer to the Bellafill Skin Test Instructions for Use.

### Q: HOW IS BELLAFILL INJECTED?

A: Bellafill is injected underneath the wrinkle, and/or acne scar just above the skin's fat layer. Bellafill provides the soft, supportive foundation that your skin needs for lasting correction.

### Q: HOW LONG DOES BELLAFILL LAST?

A: In the U.S. clinical studies Bellafill correction was maintained throughout the course of the 12-month studies.

## 3. INDICATION/INTENDED 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.

## 4. SAFETY

### Q: CONTRAINDICATIONS

A: It's important that you share your medical information with your doctor. Together, you can make an informed decision as to whether Bellafill is right for you. In order to avoid complications and unsatisfactory results, Bellafill should not be used in those who:

- Have a positive reaction to the Bellafill skin test.
- Have a history of severe allergies and **hypersensitivity (anaphylaxis)**.
- Are allergic to the anesthetic (**lidocaine**) in Bellafill.
- Have a history of allergies to any **bovine collagen** products.
- Are undergoing or planning to undergo **desensitization** injections to meat products.
- Have bleeding disorders.
- Are seeking lip augmentation
- Are prone to irregularly shaped scars that progressively enlarge (**keloid**) and thick scarring (**hypertrophic**) formation.

**Q: WHAT ARE SOME WARNINGS TO CONSIDER**

**A:** It's important that you share your medical information with your doctor. Together, you can make an informed decision as to whether Bellafill is right for you. Because use could result in significant injury, Bellafill should not be used in the following cases:

- 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 performed and the results graded before injection of Bellafill. Patients with a positive skin test or 2 skin tests with no local skin reactions but some systemic reactions should not be treated. Patients with **antibodies to bovine collagen** outside of the normal range at baseline also should not be treated. Refer to the Bellafill Skin Test Instructions for Use.
- Use of Bellafill on skin with an active inflammatory process (skin eruptions such as cysts, pimples rashes, or hives) or infection should be delayed until the inflammatory process is gone.
- Bellafill must not be injected into blood vessels. Localized tissue death and/or scarring may occur after injection in or near blood vessels, such as in the lips, nose, or the area between the eyebrows and above the nose. This is thought to result from the injury or blockage of blood vessels.
- As with all dermal filler procedures, Bellafill should not be injected in areas with many blood vessels. For example, use of similar products around the nose or between the eyebrows and above the nose has caused cases of blood vessel injury or blockage resulting in changes in sight or blindness. For additional information please see the Post-Marketing Surveillance Section.

**Q: ARE THERE ANY FURTHER PRECAUTIONS TO CONSIDER?**

**A:** Yes, you should know:

- The safety of injecting greater amounts than 3.5 mL (~3/4 of a teaspoon) per treatment site or 8.9 mL (~1 3/4 of a teaspoon) 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 has not been studied 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 (such as redness, pain, lumps/bumps, swelling) in subjects less than 36 years old (30 subjects) was similar to the incidence in subjects above the age of 36 (113 subjects). Most of these injection site reactions were mild in severity.
- The safety in patients who might develop **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 dark brown and black skin was similar to that reported in 109 patients with

white, to moderate brown skin. No occurrences of hyper or **hypopigmentation**, **hypertrophic** scarring or **keloid** formation were observed in any subjects.

- The safety of Bellafill in patients with diseases with an overactive immune system such as lupus has not been established.
- Bruising or bleeding may occur at Bellafill injection sites. Use of Bellafill in patients who have undergone blood thinner or anticoagulant treatments (for example, Warfarin or Aspirin) within 3 weeks before Bellafill injection 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 causing an inflammatory reaction at the implant site. This also applies if Bellafill is injected before the skin has healed completely after such a procedure.
- Bellafill has only been studied for injection in the skin to correct nasolabial folds and acne scars on the cheek. 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 loose skin has not been studied and the cosmetic results for these patients are unknown.
- The safety of Bellafill use during pregnancy and in breastfeeding women has not been studied.
- The safety of Bellafill in patients with connective tissue disorders (for example, rheumatoid arthritis) has not been studied.

## 5. RISKS

### Q: WHAT ARE POSSIBLE SIDE EFFECTS?

#### ***Nasolabial Fold: Adverse Events:***

Adverse events that were reported in greater than 1 % of the 391 Bellafill treated subjects who participated in the **Nasolabial Fold** Studies are listed below. The majority of the events were mild to moderate in severity

Lumpiness at the injection area occurred in 13/391 subjects. Seven (7) events occurred more than one month after injection and 6 events occurred three months after injection. Duration varied from 4 weeks to unresolved or unknown at 26 weeks. Persistent swelling or redness occurred in 13/391 subjects. Two (2) events occurred 3 months after treatment, duration varied from 5 weeks to unresolved or unknown at 26 weeks. Increased sensitivity occurred in 7/391 subjects. Two (2) events occurred three months after treatment, duration varied from 4 weeks to unresolved or unknown at 26 weeks. Rash or itching occurred in 5/391 rash, itching more than 48 hours after injection duration varied from 3 weeks to 6 weeks.

#### ***Acne Scar: Physician Diagnosed Adverse Events:***

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.

46/143 (32%) of Bellafill and 16/50 (32%) of Control subjects experienced at least one all cause (related and unrelated) Treatment-Emergent Adverse Event.

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.

Note: Please also review the product label in consultation with your treating physician.

**Patient Diary Cards reported the following short-lived events:**

Redness (**erythema**), swelling, bruising, pain, itching, lumps/bumps and discoloration. When these events were reported by subjects, the majority were mild and most resolved with two weeks.

The events that happened most often in subjects in the clinical study after the Bellafill treatment were swelling (69.2%), redness (**erythema**) (66.2%), pain (63.8%), bruising (59.2%), lumps/bumps (57.7%), itching (25.4%) and discoloration (21.5%). Most of these events (41.5%) were mild and resolved in an average of one week.

In the pivotal Acne Scar study the incidence of injection site reactions was similar in subjects under the age of 36 compared to subjects above the age of 36. The majority of these injection site reactions were mild in nature.

## 5. POST MARKETING SURVEILLANCE

Since product approval, the adverse events received via Bellafill post-marketing surveillance in on-label or off-label settings have been infrequent. Those events that occurred more than five times included (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 ranged from the event stopping to an event still 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 Bellafill injection into the blood vessel have been reported. Symptoms ranged from possible skin discoloration to bumps to skin death/scarring. Time of onset, (when known), ranged from the day of injection to 3 days after treatment. The majority of these adverse outcomes were mild in severity and no events were reported as serious. Treatments included nitroglycerin paste, aspirin, and warm compresses. These events stopped or were -improving 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 that 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 case, the product was injected into the area, which is outside the recommendation Indications for Use (see Warnings section).

## 6. ABOUT THE PROCEDURE

### **Q: What are the serious side effects?**

**A:** Rarely, the doctor may inadvertently inject the product into a blood vessel, which can cause injury to the blood supply and damage to the skin. A single case of vision abnormality has been reported with Bellafill.

Rarely, patients may develop infections that must be treated with antibiotics or other treatment.

### **Q: What should patients do prior to treatment?**

**A:** A negative Bellafill skin test is required as prior to treatment. A skin test is a safety precaution to make sure that you are not allergic to the bovine collagen or the anesthetic in Bellafill.

If you have previously suffered from facial cold sores, there is a risk that you could have another occurrence. Speak to your physician about how you may be able to prevent this with medication.

To help prevent bruising, avoid using St. John's Wort, high doses of Vitamin E supplements, fish oil supplements, omega-3 supplements, aspirin, and other non-steroidal anti-inflammatory medications, such as ibuprofen 3 weeks prior to treatment, because these may increase bruising or bleeding at the injection site. Discuss with your doctor if you are on blood thinners as these may increase chance of bruising/ bleeding or if you are on immunosuppressive therapy as this may increase the risk of infections.

### **Q: What is the dose of Bellafill?**

**A:** The amount of Bellafill you may need for treatment will depend upon the severity of your wrinkles or acne scars. Your doctor can help estimate how much Bellafill will be required. Based on the pivotal clinical studies performed, a maximum total dose of 5.8 mL (~3/4 of a teaspoon) and 8.9 mL (~ 1 3/4 of a teaspoon) can be administered for the correction of acne scars and **nasolabial folds**, respectively.

### **Q: Is one treatment enough to get the look I want?**

**A:** Most people get the results they want with one to three treatments, depending on the depth and severity of the wrinkles and/or acne scars. When you have your follow-up appointment, you and your doctor can decide if you would like further correction with Bellafill. Your doctor can tailor your treatment program to meet your individual needs. This personalized approach helps to ensure that you get the look and result you desire.



**Q: Do the injections hurt?**

**A:** As part of the subject diary cards, redness (**erythema**), swelling, bruising, pain, itching, lumps/bumps and discoloration were recorded. When these events were reported by subjects, the majority were mild and most went away in two weeks.

The events that happened most often in subjects in the Acne Scar clinical study after the Bellafill treatment were swelling (69.2%), redness (**erythema**) (66.2%), pain (63.8%), bruising (59.2%), lumps/bumps (57.7%), itching (25.4%) and discoloration (21.5%). Most of these events (41.5%) were mild and went away in an average of one week.

**Q: How much does Bellafill treatment cost?**

**A:** Bellafill is a customized treatment. Your doctor can give you the best estimate based on your specific needs.

**Q: Are there post-treatment instructions to follow after a Bellafill treatment?**

**A:** Please observe the following after treatment with Bellafill:

- An ice pack or cold compress may be used immediately after treatment to reduce swelling.
- Avoid touching the treated area within six hours following treatment. After that, the area can be gently washed with soap and water.
- Avoid exposure of the treated area to intense cold or heat such as sun lamps or direct sun until any redness of swelling has gone away.

## **7. TROUBLESHOOTING:**

**Q: When should I call my doctor?**

**A:** Most side effects like redness (**erythema**), swelling, bruising, pain, itching, lumps/bumps and discoloration will usually go away within one to two weeks. Call your doctor if you have persistent problems beyond 14 days.

Blisters or skin sores that recur may signal the presence of a herpes infection that should be treated.

If you experience any signs of infection such as fever, redness that spreads to surrounding areas, drainage, increasing tenderness or increasing pain that does not go away you should call your doctor as you may need treatment with antibiotics.

## **8. CLINICAL STUDIES:**

**Q: WHAT CLINICAL STUDIES WERE CONDUCTED ON BELLAFILL?**

**A:** Suneva Medical (and formerly Artes Medical) conducted three clinical studies in the United States to demonstrate the safety and effectiveness of Bellafill. Two studies were conducted for the use of Bellafill to correct wrinkles known as smile lines. And one study was performed for the use

of Bellafill to correct facial acne scars on the cheek.

Clinical Study #1: In this open label safety study, both the doctors and the patients knew that Bellafill was being injected. This multi-center study reviewed the safety of Bellafill injections for the correction of facial wrinkles. 157 patients were enrolled and monitored at 3, 6, and 12 months after treatment. 126 out of the 157 patients (80%) completed the 1-year study. The safety data from this study was combined with the safety data from Clinical Study #2 to define the safety record for Bellafill.

Clinical Study #2: A controlled study conducted at 8 research clinics compared the safety and efficacy of Bellafill and a commercially available collagen implant for the treatment of facial wrinkles in a total of 251 patients. The patients were randomly divided into two groups with 128 patients receiving Bellafill and 123 receiving collagen injections. After 6 months, the effect of Bellafill was compared to the effect of collagen. Photographs were taken of all of the treated wrinkles at each office visit, coded to hide patient name (and treatment), and then evaluated by a separate group of doctors who were not involved in treating the patients. These doctors evaluated the coded photographs using a wrinkle severity scale to grade the effectiveness of both the Bellafill and Control collagen results. Safety was evaluated by comparing the number and severity of side effects between the two groups.

One month after treatment, both Bellafill and the control collagen had a similar effect on improving the wrinkle. At the 3 month evaluation, Bellafill maintained its effect while the control collagen had a lesser effect. At the 6 month evaluation, Bellafill had maintained its effect while the Control group had lost its effect. This was the primary endpoint point at which effectiveness was determined. At the 12-month evaluation, Bellafill had maintained its effect. Safety was also evaluated up to 12 months after treatment. No evaluation was performed at 12 months after treatment for the Control group subjects.



Figure 1: Photographs from Clinical Study # 2 showing results at 6 and 12 months after treatment.

Clinical Study #3: 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.

The effectiveness was determined by the number of subjects who were successes at 6 months

(that is 50% or more of their treated scars improved by 2 or more points, measured by a blinded doctor using a 4-point Acne Scar Rating Scale (ASRS). The ASRS scale goes from minimal to severe scars (that is the depth of individual scars).

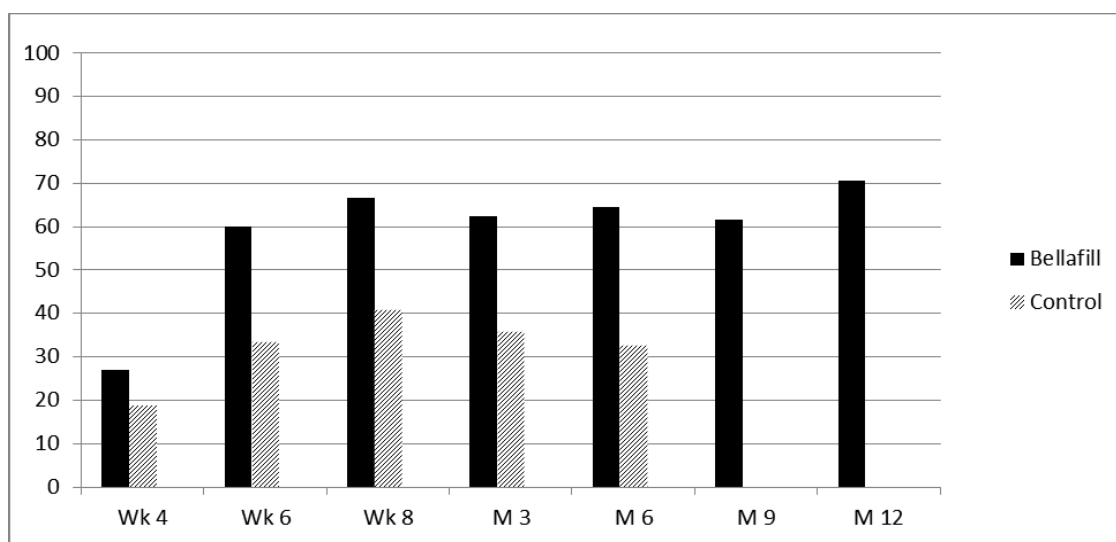
## Results

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%).

Bellafill was found to be effective (superior to Control) in patients with all colors of skin, and for male subjects as well as female subjects.

A secondary effectiveness endpoint was an ASRS measurement (using the same type of analysis) at each time point by a live blinded physician. The 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.

Subjects blinded to the treatment rated the overall degree of improvement in their treated scars using a five point, 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.

Some close up examples of the results seen in this study are shown in the photographs below.



Figure 2: Photographs from ~~Acne Scars~~ Clinical Study #3 showing results at 6 and 12 months after treatment.

### ***Physician Diagnosed Treatment Related Adverse Events – Acne Scar Study***

Fourteen (14) treatment-related adverse events were observed. 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.

## **9. USER ASSISTANCE INFORMATION**

Bellafill is only available through licensed doctors. To find a doctor who provides Bellafill near you, please visit [www.Bellafill.com](http://www.Bellafill.com) or call toll free (1-888-278-3345) in the United States or Canada. Outside of the United States or Canada, call +1-858-550-9999.

[customersupport@sunevamedical.com](mailto:customersupport@sunevamedical.com)

[www.sunevamedical.com](http://www.sunevamedical.com)

[www.bellafill.com](http://www.bellafill.com)



© 2014 Suneva Medical, Inc.  
Bellafill<sup>®</sup> mark is owned by Suneva Medical, Inc.  
Part Number: XXXX RevXX (Date: MM/YYYY)