PROTOCOL

A Pilot Study to Evaluate the Safety and Effectiveness of Microneedling and Bellafill® to Treat Facial Acne Scars

Protocol Number: SUN-15-03

Version 1.0 (11-Sep-2015)

Study Sponsor:
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CONFIDENTIAL

PROTOCOL APPROVAL PAGE

The following individuals approve this version of Protocol #SUN-15-05. All changes to this version of the protocol must have prior written approval and require an amendment or administrative letter.

Suneva Representative:

Jwala Karnik MD, Chief Medical Officer

Signature:_____ Date: _____

ethica CRO Representative:
Murray Jensen, MSc
Director of Clinical and Scientific Affairs

Signature:_____ Date: _____

INVESTIGATOR SIGNATURE PAGE

I agree to:

☐ Implement and conduct this study diligently and in strict compliance with the protocol, ICH-GCP Guidelines, and all applicable laws and regulations.

☐ Maintain all information supplied by the Sponsor or its designate in confidence and, when this information is submitted to an Institutional Review Board (IRB) or another group, it will be submitted with a designation that the material is confidential.

I have read this protocol in its entirety and I agree to all aspects.

Investigator Printed Name	Signature	Date
Investigator Printed Name	Signature	Date
Investigator Printed Name	Signature	Date

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GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
ASAS	Acne Scar Assessment Scale
CFR	U. S. Code of Federal Regulations
eCRF	Electronic Case Report Form
CRO	Contract Research Organization
CTR	Common Treatment Responses
FDA	Food and Drug Administration
GCP	Good Clinical Practices
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB	Independent Review Board
ITT	Intent to Treat
NSAID	Non-steroidal anti-inflammatory drug
PGAIS	Physician Global Aesthetic Improvement Scale
PMMA	Polymethylmethacrylate
QoL	Quality of Life
SAE	Serious Adverse Event
SAS	Statistical Analysis Software
SDs	Source Documents
SGAIS	Subject Global Aesthetic Improvement Scale
UADE	Unanticipated Adverse Device Effects
UPT	Urine Pregnancy Test
WOCBP	Women of Child Bearing Potential

PROTOCOL SYNOPSIS

Title	A Pilot Study to Evaluate the Safety and Effectiveness of Microneedling and Bellafill® to Treat Facial Acne Scars
Study Device	Bellafill®
Study Objective	To evaluate the effectiveness and safety of atrophic acne scar treatment that sequentially employs microneedling followed by Bellafill injections.
Study Population	Male and female subjects ≥21 years of age with ≥4 distensible atrophic acne scars located in the facial area that, in the Investigator's opinion, are correctable.
Study Design	Open-label, randomized, multicenter, prospective pilot study.
Number of Sites	Approximately 9 sites.
Number of Subjects	Approximately 45 subjects.
Treatment Groups	Group A: Microneedling and Bellafill. Group B: Microneedling.
Duration of Study	The duration of the study is approximately 12 months.
Inclusion Criteria	1. Outpatient, male or female subjects of any race, 21 years of age or older. Female subjects of childbearing potential must have a negative urine pregnancy test result at Baseline and practice a reliable method of contraception throughout the study. 2. Negative response to the Bellafill Skin Test. 3. Presence of ≥4 distensible atrophic acne scars (treatment scars) in the facial area. 4. Subjects with a history of HSV-1 (oral herpetic outbreak) willing to accept prophylactic treatment with antiviral medication. 5. Subject desires correction of his/her atrophic acne scarring. 6. All Fitzpatrick skin types are eligible. 7. Willing to withhold additional aesthetic therapies to the proposed treatment area (e.g., other soft tissue fillers such as hyaluronic acid, and/or any resurfacing procedures (as described in Protocol Section 5.3) for the duration of the study. 8. Able to follow study instructions and likely to complete all required visits, as assessed by the Investigator. 9. Sign an IRB-approved Informed Consent Form, Photographic Release Form, and the Authorization for Use and release of Health and Research Study Information (HIPAA) Form prior to any study-related procedures being performed.
Exclusion Criteria	1. Female subjects that are pregnant (positive urine pregnancy test), breast-feeding, or who are of childbearing potential and not practicing a reliable method of birth control. 2. Undergone facial treatments with any prohibited treatment/procedures and/or use of any other prohibited treatment/procedure within certain time periods as listed in Protocol Section 5.3. 3. Excisional facial surgery (such as Blepharoplasty, Face Lift, Rhinoplasty) of the face ≤ 6 months prior to study enrollment or plans for facial surgery

	during the study. 4. History of bleeding disorders. 5. Presence of any skin pathology or condition that could interfere with the evaluation of the treatment areas, worsen due to the proposed treatment or require interfering topical, systemic or surgical therapy. 6. Recent or current history of inflammatory skin disease, infection, cancerous/pre-cancerous lesion, unhealed wound or clinically significant acne in the proposed treatment areas. Clinically significant acne is defined as a patient whom has ≥3 active inflammatory acne lesions in the treatment areas. 7. History of systemic granulomatous diseases active or inactive (e.g., Sarcoid, Wegeners, TB) or connective tissue diseases (e.g., lupus, dermatomyositis). 8. Hypertrophic acne scars, any evidence of keloid scarring in the treatment area. 9. Known hypersensitivity or previous allergic reaction to any of the components of the study device (including lidocaine or any amide-based anesthetic), or has a history of allergies to any bovine collagen products, including but not limited to injectable collagen, collagen implants, hemostatic sponges, and collagen-based sutures. 10. Undergone or be planning to undergo desensitization injections to meat products. 11. Unable to communicate or cooperate with the Investigator due to a language barrier (non-English speaking), poor mental development, or impaired cerebral function. 12. Evidence of alcohol or drug abuse (Investigator opinion), or history of poor cooperation, non-compliance with medical treatment, or unreliability. 13. Use of an investigational device, biologic or drug in the past 30 days, or be currently participating in an experimental drug, biologic or device trial. 14. Exhibits additional physical attributes which prevent the assessment or treatment of the atrophic scars, as judged by the Investigator, such as excessive hair, traumatic or surgical scars, excessive hyperpigmentation in the treatment area, etc. 15. Has a condition or be in a situation that, in the Investigator's opinion, may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study. 16. An employee (or a relative of an employee) of the Investigator, Sponsor or representative of the Sponsor.
Study Measurements	**Effectiveness:** • Acne Scar Assessment Scale (ASAS): a validated 5-point static scale assessing physician impression of acne scar severity. • Physician Global Aesthetic Improvement Scale (PGAIS): a 5-point dynamic scale assessing cosmetic improvement. • Subject Global Aesthetic Improvement Scale (SGAIS): a 5-point dynamic scale assessing cosmetic improvement. • Subject QOL Impact Scale: (33 questions): a 33-question survey that allows the subject to specifically address how acne scarring has affected his/her emotional and functional status. **Safety:** • Adverse events: rate of AEs, type of AEs, relationship of AEs to Bellafill.

Study Procedures	The study is divided into two study Periods. In **Period I**, subjects will attend a Screening visit (Week -4) and undergo the Bellafill skin test. At Visit 1 (Day 0), all subjects will commence microneedling treatment for their atrophic acne scars. Subjects will then return to the clinic at Week 3 and Week 6 (Visits 2 and 3, respectively) for follow-up evaluation and additional cycles of microneedling treatment. At Week 12 (Visit 4), all subjects commence **Period II** and are randomized to Bellafill Treatment (Track A) or to No Treatment (Track B): • **Track A:** Consists of three (3) study visits. At Visit 4, subjects randomized to the "Bellafill" group will complete visit evaluations and then receive treatment with Bellafill for their atrophic acne scars. Subjects return for Visit 5A (Month 1 after randomization) for evaluation and follow-up, and will receive touch-up injections with Bellafill to achieve optimal correction (if necessary). Subjects will then be followed-up at Visits 6A and 7A which will occur at Month 3 and Month 6, respectively, after their last Bellafill treatment. • **Track B:** Consists of one (1) study visit. At Visit 4, subjects randomized to the "No Treatment" group will complete visit evaluations and then return for follow-up at Visit 5B (approx. Month 3 after randomization).
Sample Size Justification	This is a pilot study and a formal sample size justification is not provided. It is the opinion of the Sponsor that a total of 45 subjects will be sufficient to achieve the objectives of the study.
Statistical Methods	Statistical analyses will be conducted on an ITT basis (i.e., all enrolled subjects that have fully passed screening and have received initial microneedling treatment will be included in the analyses). Descriptive statistics (i.e., mean, standard deviation, etc.) will be provided for all continuous variables and frequencies for all categorical variables collected in this study. When appropriate, exploratory inferential statistical analyses will be conducted using SAS® software (9.3 or higher). Comparisons between treatment groups will be performed using parametric or non-parametric testing, as appropriate. The level of significance will be fixed at 0.05. No adjustments for multiplicity will be performed.

1. Background and Rationale

Acne scars occur when acne lesions become large enough that the amount of localized inflammation overcomes the skin's ability to heal normally. Dermal collagen is damaged and resorbed, leaving defects that are manifested as concavities in the skin surface.. There are two general categories of Acne Scars; ***atrophic or depressed*** *(depressions and valleys in the skin with resulting shadowing), and* ***hypertrophic or raised*** *(firm, raised papules or nodules on the skin).*[1]

Typically, over 90% of the U.S. population experiences the onset of acne during puberty and teen years[2] with some women experiencing episodes in the late 20's through their 40's due to hormonal changes.[3] A significant percentage will go on to have long term or extensive acne scarring,[1] 90% of which are atrophic acne scars and the remaining 10% hypertrophic or some mix of both scars.[4] The most commonly used descriptors for atrophic scars fall into the following categories.[5]

- ***Ice Pick*** *- Deep, narrow sharply marginated scars which resemble how the skin might look if injured with an ice pick.*
- ***Rolling or Distensible*** *- More superficial scars with rolled edges that blend more gently into surrounding normal skin.*
- ***Boxcar*** *- Sharply marginated depressions with a flat bottom, broader than Ice Pick scars.*

1.1 Incidence and Severity of Acne Scarring

There is no definitive source of data that clearly shows how many people are afflicted with each type of scar in the U.S. However, based on the few published studies found in the peer-reviewed literature and following discussions with our clinical advisors, Suneva Medical Inc. has developed a general picture of how many people are afflicted.

With regard to scar type, between 60 to 75% of the people with acne scars will have a form of rolling or distensible scar as their predominant scar type with roughly 5 to 10% having mostly boxcar scars. The remaining 15 to 20% will have ice pick scars as their most common scar finding.[6] Most individuals with acne scarring will have a mixture of two or more types of depressed scars.

Severity is challenging to define due to irregularities in the scar depression and the large range in the shape and size of acne scars. In general, studies suggest that mild scarring occurs in roughly 60 to 70% of people with scars, moderate scarring occurs in 15 to 25% and 5 to 15% of people with scars suffer from severe scarring.[7]

1.2 Treatment of Acne Scarring with Bellafill

Bellafill has been proven to be safe and effective in improving the appearance of atrophic acne scars by raising the base of the scar so that it is level with the surrounding skin. Based on a pivotal double-blinded, randomized, placebo-controlled study, the FDA approved Bellafill for the correction of acne scars in December 2014.

The study required a high threshold for success in which the primary effectiveness endpoint was proven superior for subjects treated with Bellafill compared to Control at 6 months. At 6 months, the response rate for Bellafill was 64% vs. 33% for Control (p=0.0005). Bellafill continued to show effectiveness by an unblinded assessment at 12 months (71%). A responder was defined as a subject in whom ≥50% of treated acne scars improved by ≥2 points on the validated 4-point Acne Scar Rating Scale (ASRS).

On the Physician Global Aesthetic Improvement Scale (PGAIS), 84% of subjects were rated as improved at 6 months and 98% were improved at 12 months by an unblinded assessment. On the Subject Global Aesthetic Improvement Scale (SGAIS), 77% of subjects rated their appearance as improved at 6 months and 83% rated their appearance as improved at 12 months.

1.3 Microneedling for the Correction of Acne Scarring

Microneedling involves puncturing the skin with fine, sterile needles to create small wounds in the dermis that is thought to stimulate wound healing resulting in collagen production. A mechanical device, consisting of steel microneedles in a wheel, is rolled over the surface of the skin in a patterned formation. The microneedles penetrate approximately 0.25 to 3.0 millimeters below the skins surface, and each puncture creates a channel that triggers production of new collagen and elastin, leading to improvement in the appearance of skin texture, firmness, and acne scarring. While microneedling is a popular and common procedure practice in many dermatological clinics, it has not been approved by the FDA as a treatment for acne scarring.

1.4 Current Clinical Study

A therapy that may stimulate collagen production, such as microneedling, is potentially a useful adjunct to atrophic acne scar treatment with Bellafill. The current pilot study will evaluate the effectiveness and safety of sequential treatment of microneedling followed by intra-scar injections with Bellafill.

2. Study Objective

To evaluate the effectiveness and safety of acne scar treatment that sequentially employs microneedling followed by Bellafill injections.

3. Study Design

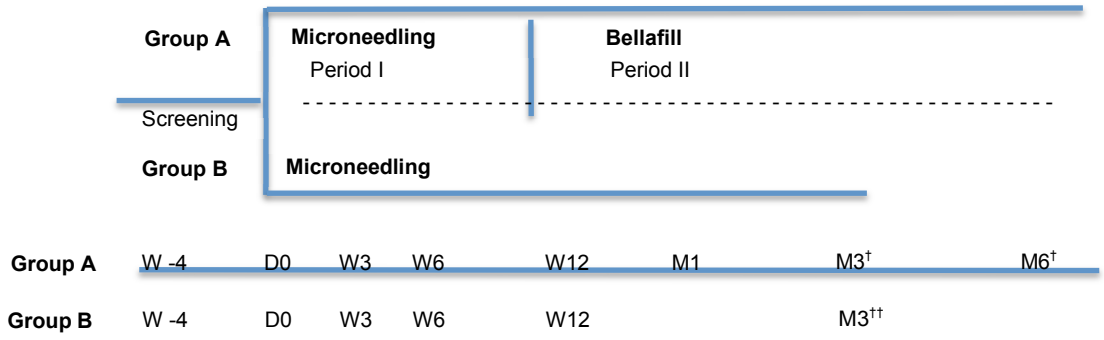
This is an open-label, randomized, multicenter, prospective trial assessing the efficacy and safety of microneedling treatment alone vs. microneedling treatment followed by treatment with Bellafill for correction of distensible atrophic facial acne scars.

The study is divided into two study Periods. In **Period I**, subjects will attend a Screening visit (Week -4) and undergo the Bellafill skin test. At Visit 1 (Day 0), all subjects will commence microneedling treatment for their atrophic acne scars. Subjects will then return to the clinic at Week 3 and Week 6 (Visits 2 and 3, respectively) for follow-up evaluation and additional cycles of microneedling treatment.

At Week 12 (Visit 4), all subjects commence **Period II** and are randomized to Bellafill Treatment (Track A) or to No Treatment (Track B):

- **Track A:** Consists of three (3) study visits. At Visit 4, subjects randomized to the "Bellafill" group will receive treatment with Bellafill for their atrophic acne scars. Subjects return for Visit 5A (Month 1 after randomization) for evaluation and follow-up, and will receive touch-up injections with Bellafill to achieve optimal correction (if necessary). Subjects will then be followed-up at Visits 6A and 7A which will occur at Month 3 and Month 6, respectively, after their last Bellafill treatment.
- **Track B:** Consists of one (1) study visit. At Visit 4, subjects randomized to the "No Treatment" group will complete visit evaluations and then return for follow-up at Visit 5B (approx. Month 3 after randomization).

3.1 Study Schematic



† Visits occur 3M and 6M after last injection of Bellafill (i.e., W12 initial treatment or M1 touch-up treatment)
†† Visit occurs 24W after D0 (i.e., approx. 3M after W12)

4. Study Population

4.1 Number of Subjects

Approximately 45 male and/or female subjects 21 years of age or older who meet the protocol's eligibility requirements will be enrolled in the study at approximately 9 investigational sites.

4.2 Study Population Characteristics

Subjects desiring correction of their acne scarring with an injectable dermal filler will be recruited for this study.

4.3 Inclusion Criteria

1. Outpatient, male or female subjects of any race, 21 years of age or older. Female subjects of childbearing potential must have a negative urine pregnancy test result at Baseline and practice a reliable method of contraception throughout the study.

   A female is considered of childbearing potential unless she is:
   - *postmenopausal for at least 12 months prior to study treatment administration; or*
   - *without a uterus and/or both ovaries; or*
   - *has been surgically sterile for at least 6 months prior to study treatment administration.*

   Reliable methods of contraception are:
   - *hormonal methods or intrauterine device in use ≥90 days prior to study treatment administration; or*
   - *barrier methods plus spermicide in use at least 14 days prior to study treatment administration; or*
   - *vasectomized partner.*

   [Exception: Female subjects of childbearing potential who are not sexually active will not be required to practice a reliable method of contraception. These subjects may be enrolled at the Investigator's discretion if they are counseled to remain sexually inactive during the study or agree to use an approved method of contraception should they become sexually active and understand the possible risks in getting pregnant during the study.]

2. Negative response to the Bellafill Skin Test.
3. Presence of ≥4 distensible atrophic acne scars located within the facial treatment area. Subject desires correction of his/her atrophic acne scarring.
4. All Fitzpatrick skin types are eligible.
5. Subjects with a history of HSV-1 (oral herpetic outbreak) willing to accept prophylactic treatment with antiviral medication.
6. Willing to withhold additional aesthetic therapies to the proposed treatment area (e.g., other soft tissue fillers such as hyaluronic acid, and/or any resurfacing procedures (as described in Protocol Section 5.3) for the duration of the study.

7. Able to follow study instructions and likely to complete all required visits, as assessed by the Investigator.
8. Sign an IRB-approved Informed Consent Form, Photographic Release Form, and the Authorization for Use and release of Health and Research Study Information (HIPAA) Form prior to any study-related procedures being performed.

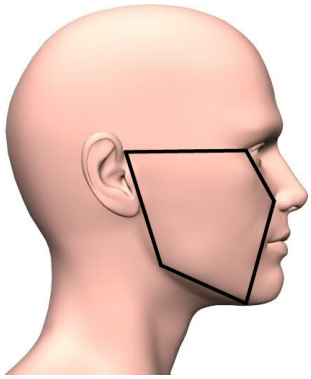
4.4 Exclusion Criteria

1. Female subjects that are pregnant (positive urine pregnancy test), breast-feeding, or who are of childbearing potential and not practicing a reliable method of birth control.
2. Undergone facial treatments with any prohibited treatment/procedures and/or use of any other prohibited treatment/procedure within certain time periods as listed in Protocol Section 5.3.
3. Excisional facial surgery (such as Blepharoplasty, Face Lift, Rhinoplasty) of the face ≤ 6 months prior to study enrollment or plans for facial surgery during the study.
4. History of bleeding disorders.
5. Presence of any skin pathology or condition that could interfere with the evaluation of the treatment areas, worsen due to the proposed treatment or require interfering topical, systemic or surgical therapy.
6. Recent or current history of inflammatory skin disease, infection, cancerous/pre-cancerous lesion, unhealed wound or clinically significant acne in the proposed treatment areas. Clinically significant acne is defined as a patient whom has ≥3 active inflammatory acne lesions in the treatment areas.
7. History of systemic granulomatous diseases active or inactive (e.g., Sarcoid, Wegeners, TB) or connective tissue diseases (e.g., lupus, dermatomyositis).
8. Hypertrophic acne scars, any evidence of keloid scarring in the treatment area.
9. Known hypersensitivity or previous allergic reaction to any of the components of the study device (including lidocaine or any amide-based anesthetic), or has a history of allergies to any bovine collagen products, including but not limited to injectable collagen, collagen implants, hemostatic sponges, and collagen-based sutures.
10. Undergone or be planning to undergo desensitization injections to meat products.
11. Unable to communicate or cooperate with the Investigator due to a language barrier (non-English speaking), poor mental development, or impaired cerebral function.
12. Evidence of alcohol or drug abuse (Investigator opinion), or history of poor cooperation, non-compliance with medical treatment, or unreliability.
13. Use of an investigational device, biologic or drug in the past 30 days, or be currently participating in an experimental drug, biologic or device trial.
14. Exhibits additional physical attributes which prevent the assessment or treatment of the atrophic scars, as judged by the Investigator, such as excessive hair, traumatic or surgical scars, excessive hyperpigmentation in the treatment area, etc.
15. Has a condition or be in a situation that, in the Investigator's opinion, may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study.
16. An employee (or a relative of an employee) of the Investigator, Sponsor or representative of the Sponsor.

5. Methods

5.1 Treatment Area

On each side of the face, the **treatment area** is defined inferiorly by the mandibular ridge and ramus, medially by the nasolabial fold and a line drawn directly inferior from the oral commissure, laterally by the tragus and pinna and superiorly by an imaginary line drawn from the lateral canthus to the top of the pinna where it attaches to the face, as per the following diagram:



5.2 Study Treatments

Microneedling Treatment: All eligible scars within the treatment areas on each side of the face will receive microneedling treatment. The device will be rolled in a horizontal direction with medium pressure. After every roll, the device will be lifted and positioned a few millimeters inferior to the previous starting point. Rolling will be repeated until the entire skin area has been treated. The device will then be reoriented vertically and rolling will be repeated in a vertical direction. See Appendix 2 for additional instructions.

Bellafill Treatment: At Visit 4, all eligible scars within the treatment areas on each side of the face will be treated. Bellafill should be injected using a standard tunneling technique whereby the filler is injected in a retrograde manner utilizing several passes until the scar reaches a desired level of correction. A touch-up treatment is allowed at Visit 5B (Month 1 after randomization) if additional treatment is required to achieve optimal correction. The total treatment volume of Bellafill used per subject is dependent on the number and size of scars treated; however, the maximal volume of Bellafill to be injected in a subject is 8.9 ml**.**

5.3 Prohibited Treatment/Procedures

Use of other soft tissue fillers in the face and/or concurrent administration of other aesthetic treatments of the face during the study are prohibited (e.g., lasers, implants, peels, microdermabrasion, etc.). Other necessary therapies that will not interfere with the response to treatment may be provided to the subject at the discretion of the Investigator.

Use of the following medications/procedures (concurrent and contraindicated treatments) have either restrictions for usage, or are prohibited during the course of the study and appropriate wash-out periods noted below must be respected:

Dermal Fillers used in the face or neck (including lips)	
! *Hyaluronic acid such as:*	
o *Juvederm, Restylane, Belotero ……*	*12 months prior to BL Visit*
o *Voluma, Restylane Lyft ……*	*12 months prior to BL Visit*
! *Hydroxylapatite……..……..…….*	*24 months prior to BL Visit*
! *Polylactic acid……...*	*24 months prior to BL Visit*
! *Porcine or human collagen* ! *Autologous fat* ! *Bellafill*	*12 months prior to BL Visit*
Prohibited Treatment: Any past use of a permanent filler or implant outside of Bellafill (e.g., polyacrylamide, polyethylene oxide, silicone)	
Systemic Medications	
! *Accutane……..*	*12 months prior to BL Visit*
! *Corticosteroiods (e.g., prednisone) or Interferon….*	*≤ 7 days pre-tx*
! *Anti-coagulation therapy (e.g., warfarin)……...*	*≤ 14 days pre-tx*
! *NSAIDs, ASA, or >30,000IU/day oral vitamin E.…*	*≤ 7 days pre-tx or ≤ 7 days post-tx*
Procedures in the face, scalp or neck	
! *Cutaneous or RF laser treatment* ! *Intense-pulsed light treatment* ! *Photodynamic therapy or Photomodulation treatment* ! *Botulinum toxin injection (injections of the trunk or extremities permitted)* ! *Prescription strength topical retinoids (tretinoin, adapalene, tazarotene)* ! *Chemical (e.g., peels) or other cosmetic procedures within treatment area(s)* ! *Excisional facial surgery (e.g., blepharoplasty, face lift, rhinoplasty)*	*6 months prior to BL Visit*
Investigational Drugs/Devices	*30 days prior to BL Visit*

All treatment/procedures received by the subject within 30 days prior to the baseline visit and throughout the treatment period must be recorded in the electronic Case Report Form (eCRF) with end dates, if applicable.

If prohibited therapies are administered during the study period, subject participation will not automatically be discontinued. The event will be documented by the site staff as a protocol deviation, and depending upon the nature of the prohibited therapy and the timing relative to the determination of the primary endpoint, the Sponsor may make a decision to discontinue the subject.

The decision to administer a prohibited medication/treatment is done with the safety of the study subject as the primary consideration. If the permissibility of a specific medication/treatment is in question, the ethica CRO Project Manager should be contacted before the prohibited medication/treatment is administered.

6. Materials

Bellafill: Commercially available Bellafill and Bellafill Skin Tests will be used (see Skin Test IFU and Bellafill IFU in Appendix 3 and 4, respectively).

Microneedling Dermarollers: Commercially available microneedling dermarollers will be provided by Suneva Medical.. Length will be 1.5mm.

6.1 Packaging, Labeling and Storage

Open label commercially packaged supplies of dermarollers and Bellafill will be provided to Investigators. Bellafill is to be stored at standard domestic refrigerator temperature.

6.2 Supplies and Accountability

The Investigator or designee will take inventory and acknowledge receipt of all shipments of Bellafill and microneedling dermarollers. Bellafill and dermarollers must be kept in a locked area with access restricted to designated study personnel. The Investigator or designee will also keep accurate records of the volumes of Bellafill injected and the number of dermarollers used. Unless other arrangements are confirmed in writing, unused syringes/dermarollers will be returned to the Sponsor.

6.3 Other Study Supplies

Supplies that are unique to this study will be provided by the Sponsor (e.g., UPTs, etc.). The Investigator is responsible for routine supplies related to pre and post-treatment care (e.g., alcohol wipes, gauze, etc.).

7. Study Methods and Procedures

7.1 Informed Consent and Subject Privacy

The purpose, procedures, risks, benefits, and alternatives to study participation will be discussed with each potential subject. Prior to any study-related procedures subjects must give their written informed consent. The subject must also give Authorization for Use and Release of Health and Research Study Information (HIPAA), authorization to take identifying clinical photographs for scientific use and other written documentation required by local regulations or the reviewing IRB prior to any study-related procedures.

7.2 Procedures for Final Study Entry

A subject is considered “Enrolled” when s/he has signed the IRB-approved informed consent form (ICF) and HIPAA authorization in the presence of the Investigator or designee. The Investigator (or designee) will collect and record medical and cosmetic procedure histories, and females of childbearing potential must have pregnancy test results evaluated as negative. All subjects must also have a negative Bellafill skin test. The Investigator will assure that each subject meets the washout requirements and eligibility criteria before randomization for study treatment.

7.3 Subject Identification and Numbering

All subjects who sign an ICF will receive a 3-digit subject number, starting at 001, and issued in ascending order. This subject number will be used to identify the subject throughout the study. Subjects withdrawn from the study will retain their subject number; new subjects will be allotted a new subject number.

7.4 Randomization and Blinding

All subjects attending Visit 4 (Week 12) will be randomized to receive “No Treatment” or “Bellafill”. A computer-generated randomization schedule will link Randomization Numbers to specific treatment assignments at random on a balanced 1:1 basis. Site-specific Randomization Lists will be created for each site that contains unique and sequentially ascending Randomization Numbers. To randomize a subject and determine treatment allocation, the Investigator or delegate will refer to the lowest unused randomization number on the Randomization List.

The next eligible subject will receive the lowest available Randomization Number, allowing eligible subjects to be randomized to the study treatment sequence in

accordance with the randomization schedule. Randomization Numbers must not be omitted or reused.

This is an open-label study and blinding does not apply.

8. Efficacy Assessments

Prior to enrollment of any study subjects, the Investigators will be trained in the use of all efficacy assessment scales. Subjects will receive training on how to perform the self-assessments during the study. The following assessments will be conducted:

- ☐ Acne Scar Assessment Scale (ASAS): a validated 5-point static scale assessing physician impression of acne scar severity;
- ☐ Physician Global Aesthetic Improvement Scale (PGAIS): a 5-point dynamic scale assessing cosmetic improvement;
- ☐ Subject Global Aesthetic Improvement Scale (SGAIS): a 5-point dynamic scale assessing cosmetic improvement;
- ☐ Subject QOL Impact Scale: (33 questions): a 33-question survey that allows the subject to specifically address how acne scarring has affected his/her emotional and functional status.

See Appendix 1 for additional details regarding the assessments used in this study.

8.1 Photography

Facial photography will also be employed in this study. Baseline photographs will be used for PGAIS and SGAIS assessments. Canfield Scientific Inc. will provide each site with photographic equipment, training and an Instruction Manual prior to the start of the study.

9. Safety Assessments

Throughout the study, subjects will be instructed to report any unusual signs or symptoms to the Investigator.

The Investigator will solicit and record information about AEs, and concomitant medications, therapies and treatments. At each post-treatment visit, phone call, or e-mail contact, the Investigator (or designee) will begin by asking the subject a general, non-directed question such as ‘How have you been feeling since the last visit?’ Directed questioning and examination will then be done as appropriate. All reported AEs will be documented in the eCRF.

10. Schedule of Study Activities

Subjects must have a negative Bellafill skin test prior to receiving study treatment. Additionally, a negative screening urine pregnancy test is required for women of childbearing potential. Please refer to the following assessment schedule for additional details:

10.1 Assessment Schedule

		Period I					*Period II*			
							Track A *Bellafill*			*Track B* *No-Tx*
Visit		**Screening**	**1**	**2**	**3**	**4**	**5a**	**6a**	**7a**	**5b**
1 week = 7D *1 month = 28D*		W -4	D0	W3 ±3D	W6 ±3D	W12 ±1W	M1 ±1W	M3† ±1W	M6† ±1W	M3†† ±1W
Informed Consent		X								
Incl/Excl Criteria, Med Hx		X	X confirm							
UPT (if applicable)		X	X[1]			X[1]	X[1]			
Facial Scar Photography		X				X[1]			X	X
Bellafill Skin Test		X Placement	X Reading							
Microneedling Treatment			X	X	X					
Randomization						**R**				
Bellafill Injections *Initial injection* *Touch-up*						**I**[2]	T[3]			
Assessments	ASAS (Investigator)	X						X	X	X
	PGAIS (Investigator)					X[1]		X	X	X
	SGAIS (subject)					X[1]		X	X	X
	QoL Scar Impact Scale (subject)		X[1]						X	X
Con Meds/Procedures		X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X

† Visits to occur 3M and 6M after last injection of Bellafill (i.e., initial treatment or touch-up treatment)

†† Visit to occur 24W after Visit 1 (i.e., approx. 3M after Visit 4)

1 Assessments to be performed prior to study treatment (if applicable)

2 If randomized to Bellafill treatment

3 Bellafill touch-up injections administered as necessary

10.2 Study Period I

10.2.1 Screening Visit (W -4)

The following activities will be conducted:

- Informed Consent/HIPAA
- Subject Demographics/Medical History and Inclusion/Exclusion Criteria
- UPT (if applicable)
- Concomitant Medication/Procedures
- Facial Scar Photography
- Bellafill skin test and record the location of placement for review at the next visit
  - *If applicable, collect any AEs, if any observed immediately after skin testing.*
- ASAS
  - *Performed by the Investigator.*
- AE Assessment

10.2.2 Visit 1: Treatment Visit (D0)

The following activities will be conducted:

- Inclusion/Exclusion Criteria (confirmation)
- UPT (if applicable)
- Review skin test results and inclusion/exclusion criteria to confirm eligibility
- QoL Scar Impact Scale
  - *Performed by the subject prior to receiving microneedling treatment.*
- Microneedling treatment (see Section 5.1)
- Concomitant Medication/Procedures and AE assessment
- Provide HSV Prophylaxis with Acyclovir for subjects with a medical history of cold sores (may be provided prior to Visit 1 at the discretion of the Investigator).

10.2.3 Visit 2 and Visit 3 (W3 ± 3D and W6 ± 3D)

The following activities will be conducted:

- Microneedling treatment (see Section 5.1)
- Concomitant Medication/Procedures and AE assessment
- Provide HSV Prophylaxis with Acyclovir for subjects with a medical history of cold sores.

10.2.4 Visit 4 (W12 ± 1W)

The following activities will be conducted:

- Concomitant Medication/Procedures and AE assessment
- UPT (if applicable)
- PGAIS
  - *The Investigator will refer to Baseline photographs for PGAIS evaluation.*
- SGAIS
  - *The subject will refer to Baseline photographs for SGAIS evaluation.*
- Facial Scar Photography
- Randomization
  - *Subject allocated to Track A (Bellafill Treatment) or Track B (No Treatment) as per Section 7.4.*
- Bellafill injections – Subjects randomized to Track A only
  - *Document the number of scars treated as well as the method and volume of treatment.*
- Scheduling of next clinic visit
  - *Track A: Subjects randomized to **Bellafill Treatment** attend Visit 5a at 1 Month from this visit.*
  - *Track B: Subjects randomized to **No Treatment** attend Visit 5b at 24 Weeks from Visit 1 (i.e., approximately 3 Months from this Visit 4).*

10.3 Study Period II (Track A – Bellafill Treatment)

10.3.1 Visit 5a (M1 ± 1W)

The following activities will be conducted 1M from Visit 4:

- UPT (if applicable)
- Concomitant Medication/Procedures and AE assessment

- Touch-up Study Treatment
  - *The Investigator will examine the subject and determine if touch-up treatment is required to achieve optimal correction. Previously treated scars determined to be undercorrected will receive touch-up treatment. New scars (i.e., previously untreated) may not be treated.*
  - *Document the number of scars treated as well as the method and volume of treatment.*
  - *Subjects who merit additional treatment but decline touch-up treatment will not be retreated but will continue to participate in the study if they otherwise consent to continued participation.*

10.3.2 Visit 6a (M3 ± 1W)

The following activities will be conducted 3M from Visit 4:

- Concomitant Medication/Procedures and AE assessment
- ASAS and PGAIS
  - *The Investigator will refer to Baseline photographs for PGAIS evaluation.*

10.3.3 Visit 7a (M6 ± 1W)

The following activities will be conducted 6M from Visit 4:

- Concomitant Medication/Procedures and AE assessment
- Facial Scar Photography
- ASAS and PGAIS
  - *The Investigator will refer to Baseline photographs for PGAIS evaluation.*
- QoL Scar Impact Scale and SGAIS
  - *The subject will refer to Baseline photographs for SGAIS evaluation.*
- Study Exit

10.4 Study Period II (Track B – No Treatment)

10.4.1 Visit 5b (M3 ± 1W)

The following activities will be conducted 24W from Visit 1:

- Concomitant Medication/Procedures and AE assessment
- Facial Scar Photography
- ASAS and PGAIS
  - *The Investigator will refer to Baseline photographs for PGAIS evaluation.*
- QoL Scar Impact Scale and SGAIS
  - *The subject will refer to Baseline photographs for SGAIS evaluation.*
- Study Exit

10.5 Instructions for Subjects

Prior to attending all study visits, subjects must refrain from applying facial cosmetics. Makeup may be re-applied after the study visits at the discretion of the Investigator. Subjects must avoid prolonged sun exposure to face for 24 hours prior to treatment.

Subjects should avoid strenuous exercise, NSAID products, consumption of alcoholic beverages and any exposure to sun or heat for at least 24 hours after treatment to reduce the risk of post treatment redness, swelling, and/or itching. Subjects should avoid applying sunscreen to the face for the first 24 hours following microneedling

treatment. After that period, sunscreen (UVB 30 minimum) should then be diligently applied. Subjects will also be advised not to manipulate or massage injected areas.

Subjects will be instructed to contact the Investigator or his/her research staff to report any unexpected symptoms or to ask any questions about the study.

10.6 Unscheduled Visits

Each time the subject returns to the study site the Investigator will solicit and record information about AEs, and concomitant medications, therapies and treatments. An interim or unscheduled visit may replace a scheduled visit if it occurs within the acceptable time window for a scheduled visit or if the scheduled visit was missed. All applicable procedures should be performed.

10.7 Early Discontinuation/Withdrawal

It is the right and duty of the Investigator to discontinue a subject's participation when the subject's health or well-being is threatened by continuation in the study. Such subjects should be withdrawn from the study and not continued under a modified regimen. In the event of premature discontinuation, the Investigator should determine the primary reason for discontinuation. A subject who is withdrawn from the study prior to initiation of treatment may be replaced. The following are circumstances that may result in the subject's discontinuation from the study:

- the subject experiences a serious AE rendering them unable to continue study participation; or
- the subject is unable to physically or mentally tolerate the test treatment; or
- the subject voluntarily withdraws; or
- the subject receives a prohibited therapy that could significantly confound the results.

Subjects may voluntarily withdraw from the study at any time without jeopardy to future medical care. They may also be administratively withdrawn if they fail to return for follow-up. If a subject chooses to withdraw from the study, the subject will be encouraged to have a final assessment and undergo the final procedures listed in the protocol.

For any subject who withdraws from the study the date and reason for withdrawal will be recorded on the eCRF. If an AE is ongoing at the time of the withdrawal, the Investigator will attempt to follow the subject until the AE has resolved or stabilized or until follow-up is no longer possible.

10.8 Lost to Follow-Up

Significant efforts will be made to encourage all subjects to complete the study. For subjects that are lost to follow-up the site will contact the subject's secondary contact if listed in the subject's medical record or the subject identification log as another means to contact the subject. If this is unsuccessful a final certified letter will be sent by the Investigator notifying the subject of the need and importance to follow-up.

10.9 Study Termination

The Sponsor reserves the right to terminate this study for any reason upon reasonable notice to the Investigators.

If conditions arise during the study that indicate that the study or an investigational site should be terminated, the Sponsor, Investigator, Monitor, IRB, and/or regulatory agencies will discuss the situation and take appropriate action after consultation.

Conditions warranting termination of the study or site include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to subjects enrolled in the study;
- The decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the study device;
- Failure of the Investigator to comply with pertinent national or state regulations, IRB-imposed conditions, or protocol requirements;
- Submission of knowingly false information from the Investigator to the Sponsor, Monitor, IRB, or any regulatory agency.

11. Adverse Events

Throughout the course of the study, all AEs will be monitored and reported through the AE eCRF. If an AE occurs, the first concern will be the safety of the study subjects. All AEs occurring after study device administration will be followed until the event has resolved or stabilized or until follow-up is no longer possible.

11.1 Definitions

11.1.1 Adverse Events (AEs)

An AE is defined as any undesirable physical, psychological or behavioral effect experienced by a subject during his/her participation in a study, in conjunction with the use of the device, whether or not it is considered procedure or product related. AEs may include, but are not limited to, subjective or objective symptoms spontaneously offered by the subject, solicited via subject interviews, uncovered by review of concomitant medications or therapies, and/or observed by the Investigator. The Investigator will record the description (sign, symptom, or diagnosis), onset, resolution, seriousness, severity, cause and action taken for any event on the AE eCRF.

Disease signs and symptoms that existed prior to the study injections are not considered AEs unless the condition recurs after the subject has recovered from the pre-existing condition or the condition worsens in intensity or frequency during the study.

Commonly-reported AEs in previous studies include the following local skin changes: skin discoloration, increased sensitivity, telangiectasias in implant area, scar, edema, erythema, abscess or infection, recurrence of a pre-existing herpes labialis, ulceration, erosion or necrosis, itching or burning, pain and/or tenderness, granuloma formation, and skin blanching. Additionally, systemic findings reported in prior studies include: drop in blood pressure or anaphylactic shock, difficulty breathing, tightness in chest, shortness of breath, immune mediated diseases, tingling, numbness, temporary pain in various areas of the body, flu-like symptoms, blurred vision, or hypersensitivity to bovine collagen. The relevance of these findings to the current Bellafill product is not known.

11.1.2 Common Treatment Responses (CTRs)

Common Treatment Response (CTRs) following the use with a dermal filler include redness, pain, tenderness, firmness, swelling, lumps/bumps, bruising, itching and discoloration. CTRs will not be recorded as AEs unless the duration and/or severity are in excess of that typically observed following injection of a dermal filler, and are clinically significant as determined by the Treating Investigator.

11.1.3 Serious Adverse Events and Unexpected Adverse Device Effects

A Serious Adverse Event (SAE) is any AE that results in any of the following:

- Death
- Life-threatening injury or illness – any AE that places the subject, in the view of the reporter, at immediate risk of death from the AE as it occurred (It does not include an AE that, had it occurred in a more severe form, might have caused death)
- Inpatient hospitalization or prolongation of existing hospitalization. However, preplanned or elective hospitalizations for pre-existing conditions that have not worsened during the course of the study should not be considered SAEs
- Persistent or significant disability/incapacity – any AE that results in a substantial disruption of the subject's ability to conduct normal life functions
- Important medical events that may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

An Unexpected Adverse Device Effect (UADE) is any device-related AE that meets one or more of the following criteria:

- Is not identified in nature, severity or frequency in current literature on the product
- Is life threatening, even if temporary in nature
- Results in permanent impairment of a body function or permanent damage to a body structure
- Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure

Also considered an UADE is any device malfunction that would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

11.1.4 Severity

Definitions for classification of severity appear below. For events reported on the AE eCRF, the Investigator will determine the severity classification based on these definitions, his/her clinical experience in the use of dermal fillers, and/or the subject's description of the event. [Note: A "severe" AE is not the same as a "serious adverse event," which is defined above.]

- Mild: Symptoms are barely noticeable or do not make the subject uncomfortable. The AE does not influence performance or functioning. Prescription drugs are not ordinarily needed for relief of symptom(s).
- Moderate: Symptoms are of sufficient severity to make the subject uncomfortable. Performance of daily activities is influenced. Tx of symptom(s) with prescription drugs or therapies may be needed.
- Severe: Symptoms are of sufficient severity to cause the subject severe discomfort. Performance of daily activities is compromised. Tx for symptom(s) with prescription drugs or therapies may be needed.

11.1.5 Relationship to Study Device

The Investigator will determine relatedness of the subject's symptom or problem to the study device or the injection procedure.

11.2 Procedures for Reporting Adverse Events

All AEs should be recorded through the AE eCRF.

11.3 Procedures for Unmasking of Study Devices

Not applicable. This is an open-label study.

11.4 Pregnancy

A female is considered a Woman of Childbearing Potential (WOCBP) unless she is postmenopausal for at least 12 months prior to study treatment administration, without a uterus and/or both ovaries, or has been surgically sterile for at least 6 months prior to study treatment administration.

In order to participate in the study, sexually active WOCBP must use one of the following reliable methods of contraception: hormonal methods or intrauterine device in use ≥90 days prior to study treatment administration, barrier methods plus spermicide in use ≥14 days prior to study treatment administration, or vasectomized partner. Non-sexually active WOCBP will not be required to practice a reliable method of contraception. These subjects may be enrolled at the Investigator's discretion if they are counseled to remain sexually inactive during the study and understand the possible risks in getting pregnant during the study.

12. Statistics

12.1 Sample Size Justification

Approximately 45 subjects will be enrolled. This is a pilot study and a formal sample size justification is not provided for this study. It is the opinion of the Sponsor that a total of 45 subjects will be sufficient to achieve the objectives of the study.

12.2 Efficacy Parameter Analysis

Statistical analyses will be conducted on an intent-to-treat (ITT) basis (i.e., all enrolled subjects that have fully passed screening and have received initial microneedling treatment will be included in the analyses). Descriptive statistics (i.e., mean, standard deviation, etc.) will be provided for all continuous variables and frequencies for all categorical variables collected in this study. When appropriate, exploratory inferential statistical analyses will be conducted using SAS® software (9.3 or higher). Comparisons between treatment groups will be performed using parametric or non-parametric testing, as appropriate. The level of significance will be fixed at 0.05. No adjustments for multiplicity will be performed.

Summary tables will be used to present population characteristics at Baseline. Data from the study questionnaires will be included. For categorical parameters, the number and percentage of subjects in each category will be presented. The denominator for percentage will be based on the number of subjects appropriate for the purpose of analysis. For continuous parameters, descriptive statistics will include n (number of subjects), mean, standard deviation, median, and range. No imputation will be used to account for missing data. No particular processing for outliers will be performed. Data will be presented as reported in the eCRF.

12.3 Safety Analysis

Safety analyses will be performed in terms of incidence and severity of adverse events. These will be tabulated and a complete listing of all reports of adverse and/or unexpected events will be presented.

Concomitant medications will be coded to generic terms. The listing will include study treatment date, start and stop date, and whether the drug was taken during study treatment.

13. Administrative Issues

This protocol will be conducted in accordance with the applicable U.S. Food and Drug Administration (FDA) regulations and guidelines and ICH-GCP Guidelines.

13.1 Protection of Human Subjects

13.1.1 Compliance with Informed Consent Regulations (21 CFR Part 50)

Written informed consent will be obtained from each subject prior to enrollment into the study (i.e., before performing any screening evaluations or procedures).

13.1.2 Compliance with Institutional Review Board Regulations (21 CFR Part 56)

This study will be conducted in accordance with IRB regulations (U.S. 21 CFR Part 56.103). The Investigator must obtain approval from a properly constituted IRB prior to initiating the study and obtain re-approval at least annually.

13.1.3 Compliance with the ICH-GCP Guidelines (ICH E6)

This protocol will be conducted in accordance with the applicable ICH-GCP Guidelines (ICH E6).

13.2 Changes to the Protocol

Strict adherence to the protocol is necessary to assure validity of the study. The Investigator must notify the Sponsor or designee and the reviewing IRB of significant deviations from this protocol. Significant deviations to the protocol will be documented and maintained as part of the study record. Lost to follow-up, out of window visits or assessments missed due to the subject's non-participation will be documented, but not considered significant deviations.

The Investigator must not implement any changes to the protocol without approval by the Sponsor and prior review and documented approval from the IRB, except where necessary to eliminate immediate hazards to study subjects, or when the changes involve only logistical or administrative aspects of the study (e.g., change of telephone numbers).

No amendments to the protocol will be implemented without the prior written consent of the Sponsor. Should an amendment be necessary, the reviewing IRB and FDA may require review and approval of it prior to implementation.

13.3 Subject Confidentiality and Privacy

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study device may ultimately be marketed, but the subject's name will not be disclosed in these documents. The subject's name may be disclosed to the Sponsor of the study (Suneva), the CRO (ethica CRO Inc.), the governing health authorities (e.g., FDA) if they inspect the study records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

Written authorization will be obtained from each subject prior to enrollment into the study in accordance with the applicable privacy requirements (e.g., the Health Insurance Portability and Accountability Act Standards for Privacy of Individually Identifiable Health Information - HIPAA).

13.4 Required Regulatory Documents

It is the responsibility of the Investigator and study staff to maintain a comprehensive and centralized filing system of all study-related documentation, which is suitable for inspection at any time by the study monitor, the IRB, and the FDA. Elements should include:

- Subject files containing the completed case report forms, supporting source documentation and the informed consent, with signatures by the Investigator or sub-Investigators.
- Pharmacy or Investigator files, containing the investigational agent accountability records or dispensation logs and all study agent related correspondence.
- Confidential disclosure agreement with the Sponsor.
- Financial disclosure forms for each Investigator or sub-Investigator.
- Study files, containing the following required documentation:
  - Protocol with all amendments
  - The Skin Test IFU (Appendix 3) and Bellafill IFU (Appendix 4)
  - Copies of all pre-study documentation and all correspondence to and from the IRB and the Sponsor or Sponsor representatives
  - An up-to-date curriculum vitae for the principal Investigator.
  - Signed and dated Investigator agreement
  - Copies of all written communications with the IRB including all approval forms.
  - A copy of the IRB approved informed consent form and other adjunctive materials (e.g., advertising) used in the study, including written documentation of IRB approval of these items.
  - In addition to the documents required prior to the study, other documentation may be required during the course of the study.

13.4.1 Source Documents

Individual subject records will be maintained in the Investigator's Source Documents (SDs). Source documentation is generally considered to be the document on which the information or data point was first recorded. SDs may include source document worksheets, a subject's medical records, hospital charts, clinic charts, and the Investigator's study files as well as the results of diagnostic tests such as X-rays, laboratory tests, and electrocardiograms.

13.4.2 Electronic Case Report Form (eCRF) Completion

Treatment and follow-up of subjects will be recorded in a 21 CFR part 11 compliant eCRF. Data will be first recorded into the medical record and study specific source document worksheets, as applicable, prior to entry into the eCRF.

The study coordinator will refer to the source document worksheets in conjunction with the medical record in order to complete data entry into the eCRF.

In order to review and electronically sign the eCRF, the Investigator will have individual login passwords that will allow them to entered data. The Investigator must ensure that they electronically sign for completed eCRFs on a timely basis.

13.4.3 Study Summary

The Investigator will submit to the Sponsor on a regular basis copies of the Study Visit Log, which lists all enrolled subjects by Subject Number, initials, and dates of completed visits. The Investigator will submit a final progress report to his/her reviewing IRB within

3 months of study completion at the site. The Investigator will also provide additional reports to the IRB or to the Sponsor upon request.

13.4.4 Retention of Documentation

Essential documents are any records that demonstrate the compliance of the subject, Investigator, Sponsor, and Monitor with the study protocol, ICH-GCP Guidelines, and with all applicable regulatory requirements. Essential documents (including but not limited to study-related correspondence, subject records, subject privacy documentation, records of the distribution and use of all investigational devices, source document worksheets and hardcopies of eCRFs) should be retained and available for audit by the Sponsor's auditor and regulatory authorities until at least 2 years after completion or termination of the study. Suneva requires that it be notified in writing if the Investigator chooses to store the records at a different physical address than the site address or if the Investigator wishes to relinquish ownership of the data so that mutually agreed-upon arrangements can be made for transfer of ownership to a suitably qualified, responsible person.

13.5 Monitoring by the Sponsor

Clinical research staff (monitors) designated by the Sponsor may visit the study center periodically to monitor adherence to the protocol and to applicable FDA regulations, and the maintenance of adequate and accurate clinical records. Monitoring functions will be performed in compliance with ICH-GCP Guidelines. The Investigator agrees to allow these personnel access to the clinical supplies, the Bellafill dispensing and storage area, subject medical records, laboratory data, and other source documentation of the study subjects.

13.6 On-Site Audits

The FDA, in the form of a trained and properly-authorized employee of the department, may request access to all study records, including source documents, for inspection and copying, in keeping with FDA regulations. The Investigator should immediately notify the Sponsor of an upcoming inspection. An auditing inspection may also be conducted by a representative of the Sponsor's Quality Assurance department.

13.7 Proprietary Information

The information generated during this study is considered to be the property of the Sponsor and cannot be used in publication without the written consent of the Sponsor.

13.8 Publications

Suneva, as the Sponsor, has a proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation among multiple Investigators and sites and Sponsor personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multi-center study except as agreed with the Sponsor.

13.9 References

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4. *Holland, D.B., Jeremy, A.H.T., Roberts, S. G., Seukeran, D.C., Layton, A.M., & Cunliffe, W. J. "Inflammation in Acne Scarring: A Comparison of the Responses in Lesions from Patients Prone and Not Prone to Scar." British Journal of Dermatology, British Association of Dermatologists, 2004.*
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7. *Lee, J.B., Chung, W.G., Kwahck, H., & Lee, K.H. "Focal Treatment of Acne Scars with Trichloroacetic Acid: Chemical Reconstruction of Skin Scars Method." Dermatol Surgery, ASDS, Blackwell Publishing, Nov 2002.*
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APPENDICES

Appendix 1: Study Assessments

Appendix 2: Microneedling Procedure

Appendix 3: Skin Test Instructions for Use

Appendix 4: Bellafill Instructions for Use

APPENDIX 1: Study Assessments

A. Acne Scar Assessment Scale (ASAS): The ASAS is a static assessment scale that allows the Investigator to measure his/her impression of acne scar severity within the treatment area. The treatment area on each side of the face will be assessed separately, then will be averaged to obtain a global score.

Term	Grade	Description
Clear	**1**	No depressions are seen in the treatment area. Macular discoloration may be seen.
Very Mild	**2**	A single depression is easily noticeable with direct lighting (deep). Most or all of the depressions seen are only readily apparent with tangential lighting (shallow).
Mild	**3**	A few to several, but less than half of all the depressions are easily noticeable with direct lighting (deep). Most of the depressions seen are only readily apparent with tangential lighting (shallow).
Moderate	**4**	More than half of the depressions are apparent with direct lighting (deep).
Severe	**5**	All or almost all the lesions can be seen with direct lighting (deep).

B. Physician Global Aesthetic Improvement Scale (PGAIS): The Investigator will refer to baseline photographs and assess global overall improvement (but without considering untreated scars) as per the following:

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

C. Subject Global Aesthetic Improvement Scale (SGAIS): The degree of aesthetic improvement will be assessed by the subject using the SGAIS as defined below. The subject will refer to baseline photographs and assess global overall improvement (but without considering untreated scars) as per the following:

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

D. Quality of Life Scar Impact Scale: The following Quality of Life Scar Impact Scale questionnaire allows the subject to specifically address how acne scarring has affected his/her emotional and functional status:

Please circle the number that best describes how you feel. Circling the number one suggests that you believe that the description on the left hand column best describes how you feel. Circling the number 7 suggests that you believe that the description on the right hand column best describes how you feel. Circling number 4 suggests that you feel neutral or that there has been no change. Please be honest.

The amount and appearance of my acne scarring causes me to feel . . .

1. Less anxious 1 2 3 4 5 6 7 More anxious
2. More optimistic 1 2 3 4 5 6 7 Less Optimistic
3. More energetic 1 2 3 4 5 6 7 Less energetic
4. Eating more healthy food 1 2 3 4 5 6 7 Eating less healthy food
5. Happier 1 2 3 4 5 6 7 Sadder
6. Exercising more 1 2 3 4 5 6 7 Exercising less
7. Less irritable 1 2 3 4 5 6 7 More irritable
8. More amorous 1 2 3 4 5 6 7 Less amorous
9. More social 1 2 3 4 5 6 7 Less social
10. More productive 1 2 3 4 5 6 7 Less productive
11. More focused 1 2 3 4 5 6 7 Less focused
12. Less tired 1 2 3 4 5 6 7 More tired
13. Less angry 1 2 3 4 5 6 7 More angry
14. More confident 1 2 3 4 5 6 7 Less confident
15. More sexually confident 1 2 3 4 5 6 7 Less sexually confident
16. More assertive 1 2 3 4 5 6 7 Less assertive
17. Less argumentative 1 2 3 4 5 6 7 More argumentative
18. More comfortable with others 1 2 3 4 5 6 7 Less comfortable with others
19. More likely to go out 1 2 3 4 5 6 7 Less likely to go out
20. More involved in community activities 1 2 3 4 5 6 7 Less involved in community activities
21. Doing better at work/school 1 2 3 4 5 6 7 Doing worse at work/school
22. More in control 1 2 3 4 5 6 7 Less in control
23. Taking more medications 1 2 3 4 5 6 7 Taking less medications
24. Less depressed 1 2 3 4 5 6 7 More depressed
25. Seen by others as less stressed 1 2 3 4 5 6 7 Seen by others as more stressed
26. Feeling more attractive 1 2 3 4 5 6 7 Feeling less attractive
27. More relaxed 1 2 3 4 5 6 7 Less relaxed
28. Happier when looking in mirror 1 2 3 4 5 6 7 Less happy looking in mirror
29. Using less cosmetics to hide scars 1 2 3 4 5 6 7 Using more cosmetic to hide scars
30. Happier when my face is touched 1 2 3 4 5 6 7 Less happy when my face is touched
31. My life is better 1 2 3 4 5 6 7 My life is worse
32. Drinking more alcohol 1 2 3 4 5 6 7 Drinking less alcohol
33. Happier with my body 1 2 3 4 5 6 7 Less happy with my body

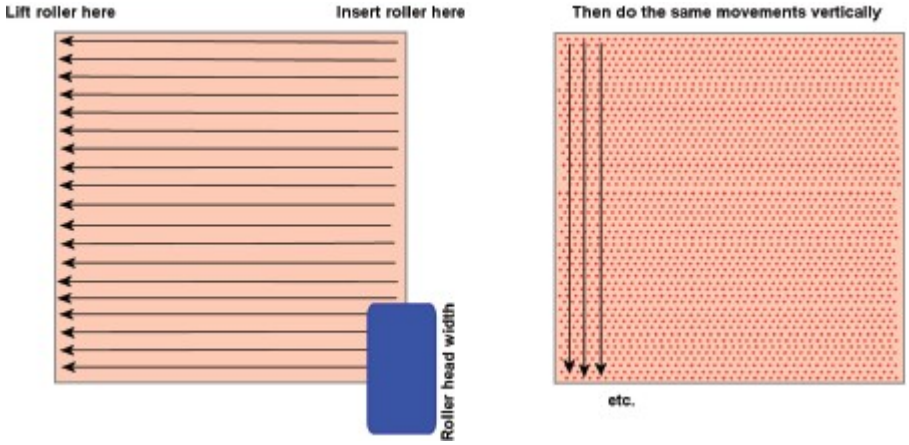
APPENDIX 2: Microneedling Procedure

Pre-skin Treatment

- Exfoliate the skin with a microderm abrasion brush.
- Wash and rinse the skin, pat dry.
- Sterilize the microneedling device per the manufacturer's recommendations.
- Provide anesthesia to the skin surface using a topical anesthetic for up to 30 minutes and/or topical ice pack.
- Remove anesthetic and swab skin with alcohol.

Rolling Technique

- Apply a layer of Regenica Repair Complex to the treatment area before applying the needling device. This will help the needles glide smoothly over the surface of the skin and prevent additional trauma.
- To achieve a uniform distributed prick density, the best recommended approach is to begin rolling in a horizontal direction, and after every roll with medium pressure, lift the roller and position it a few millimeters from the previous starting point, repeating the rolling movement until the entire skin area has been treated.
- When the treatment is complete, apply another layer of Regenica Repair Complex to the region and repeat the process similarly in a vertical direction.
- When rolling, stretch the skin by pulling it with the opposite hand to facilitate needle penetration.
- Most important is to *lift the roller* after each rolling motion, rather than rolling back and forth, to prevent a high skin prick density along the same area. Please see the diagram below:



- Perform rolling on the cheeks, and avoid the orbit and lips.
- Rolling diagonally or back-and-forth produce undesirable effects.
- *Rolling diagonally is **not recommended***. This is not the optimal technique because the center of the diagonal pattern gets a much greater skin prick density than the periphery. A perfectly uniform prick density can only be achieved when rolling at straight angles, such as in a horizontal or vertical direction.

- *Rolling back-and-forth without lifting the roller is also **not recommended** due to extreme prick density distributed over narrow "bands".* If the roller is not lifted after each rolling movement, the roller will resist sideway movements because of the needles in the skin, producing a "railway effect" as a train on a track. Moving back and forth produces the same skin pricks, causing a high prick density or larger-diameter of pricks in the skin.

Post-rolling Treatment

- Erythema typically resolves in 12 hours.
- Place an ice pack if needed for pain.
- Moisturize the skin with Vitamin A & C, and/or Aloe Vera afterwards. Moisturize with a non-irritating moisturizer.
- Apply sunscreen daily, and only after 24hrs post-microneedling treatment

After-use Disinfection of the Microneedle Instrument

- Sterilize the microneedling device per the manufacturer's recommendations; use an appropriate detergent since alcohols do not dissolve proteins as found in blood and skin

APPENDIX 3: Skin Test Instructions for Use

bellafill® SKIN TEST INSTRUCTIONS FOR USE

DESCRIPTION

Bellafill® Skin Test is an aseptically produced device composed of purified collagen gel. Each Bellafill® Skin Test consists of 3.5% bovine collagen, 2.7% phosphate buffer, 0.9% sodium chloride, 0.3% lidocaine hydrochloride, and 92.6% water for injection.

INDICATIONS

Bellafill® Skin Test is intended to be administered intradermally into the volar forearm to identify individuals who might show hypersensitivity to injectable bovine dermal collagen devices. Patients so identified are ineligible for treatment with Bellafill®.

CONTRAINDICATIONS

- Bellafill® Skin Test contains bovine collagen and is contraindicated for patients with a history of allergies to any bovine collagen products, including but not limited to collagen injectables (except to verify questionable allergy), collagen implants, hemostatic sponges, and collagen-based sutures, because these patients are likely to have hypersensitivity to the Bellafill® Skin Test.
- Bellafill® Skin Test is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.

- Bellafill® Skin Test contains lidocaine and is contraindicated for patients with known hypersensitivity to lidocaine.
- Bellafill® Skin Test is contraindicated for patients undergoing or planning to undergo desensitization injections to meat products, as these injections can contain bovine collagen.

WARNINGS

- If the Skin Test response is positive, the patient must not be treated with Bellafill®. If the Skin Test response is equivocal, it is recommended that a second Skin Test be administered in the opposite arm and evaluated prior to the initiation of treatment.
- Some physicians have reported the occurrence of connective-tissue diseases such as rheumatoid arthritis, systemic lupus erythematosus (SLE), polymyositis (PM), and dermatomyositis (DM) subsequent to collagen injections in patients with no previous history of those disorders. Also, an increased incidence of cell-mediated and humoral immunity to various collagens has been found in systemic connective-tissue diseases such as rheumatoid arthritis, juvenile rheumatoid arthritis, and progressive systemic sclerosis (scleroderma). Patients with these diseases may thus have an increased susceptibility to hypersensitivity responses and/or accelerated clearance of their implants when injected with bovine dermal collagen preparations. Therefore, caution should be used when treating these patients, including consideration for further skin testing.

- Patients with a history of dietary beef allergy should be carefully examined before they are administered the Bellafill® Skin Test since it is possible that the collagen component of the beef may be causing the allergy. More than 1 skin test is highly recommended prior to treating these patients.

PRECAUTIONS

- As with all transcutaneous procedures, Bellafill® Skin Test injection carries a risk of infection. The usual precautions associated with injectable materials should be followed.
- Results of the Skin Test may be inaccurate if patients are on immunosuppressive therapy.
- Bellafill® Skin Test should be used with caution in patients who are atopic or have a history of allergies. This class of patient has a greater potential of ultimately exhibiting an allergic reaction to bovine collagen than do other patients.
- Use of Bellafill® Skin Test 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 underlying process has been controlled.

ADVERSE EVENTS

Rare anaphylactoid responses have been reported with collagen implants, including acute episodes of hypotension, difficulty breathing, tightness in chest, and/or shortness of breath. On rare occasions, the hypersensitivity response has progressed to a cystic reaction which may drain purulent material.

DIRECTIONS FOR USE

Note: The Bellafill® Skin Test should be stored at standard refrigerator temperatures. DO NOT FREEZE.

Prior to being administered the Bellafill® Skin Test, the patient should be provided with a copy of the Bellafill® Skin Test Results Card. The patient should be fully apprised of the purpose of and evaluation criteria for the Skin Test.

1. After verifying that contraindications to the proposed Bellafill® treatment do not exist, a Bellafill® Skin Test is administered. At the time of the initial evaluation, a complete medical history should be obtained.

2. The Bellafill® Skin Test syringe must be brought to room temperature before injection.

3. After cleansing the site, 0.1 cc Bellafill® Skin Test should be implanted intradermally into a volar forearm surface. The results of the Skin Test must be carefully evaluated for a 4-week period prior to the initiation of treatment with Bellafill®. Patients should be instructed to notify their physicians of any untoward test response observed within the 4-week period.

4. Discard the syringe after administration of the Bellafill® Skin Test.

a. 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.

b. 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), which 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.

TREATMENT WITH BELLAFILL® IS CONTRAINDICATED IN ANY PATIENT EXHIBITING A POSITIVE RESPONSE OR 2 EQUIVOCAL RESPONSES.

Clinical experience has shown that the importance of screening by means of the Bellafill® Skin Test cannot be overemphasized. However, a negative Skin Test does not preclude the possibility of the

HOW SUPPLIED

Bellafill® Skin Test is an aseptic product packaged in configurations of 2 or 5 syringes in one sealed tray per box. Each syringe contains 0.3 cc of purified collagen gel. Each Bellafill® Skin Test consists of 3.5% bovine collagen, 2.7% phosphate buffer, 0.9% sodium chloride, 0.3% lidocaine hydrochloride, and 92.6% water for injection. Bellafill® Skin Test syringes are appropriate only for testing prior to treatment with Bellafill®.

Each syringe is sealed for single-patient use. The tip of the syringe is sealed with a tamper-evidence cover. The tray lid is also sealed with a tamper-evidence cover. Do not use if package is damaged or the cover is broken or removed. Do not resterilize.

STORAGE DIRECTIONS

Bellafill® Skin Test syringes should be stored at standard refrigerator temperatures. DO NOT FREEZE.

Bellafill® Skin Test has a clear appearance. In the event that a syringe does not have a clear appearance, do not use the syringe, and notify Suneva Medical at 844-BELLAFILL (844-235-5234). Outside the United States, call ++1-858-550-9999.

To place an order, contact Suneva Medical, Inc. In the United States, call toll-free: 844-BELLAFILL (844-235-5234).
Outside the United States, call ++1-858-550-9999. Orders may also be sent by fax to 858-550-9997, or email to orders@sunevamedical.com.

Caution: Federal law restricts this device to physician use only.

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APPENDIX 4: Bellafill Instructions for Use

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.
- Introduction of product into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. Take extra care when injecting soft tissue fillers, for example inject the product slowly and apply the least amount of pressure necessary. Rare but serious adverse events associated with the intravascular injection of soft tissue fillers in the face have been reported and include temporary or permanent vision impairment, blindness, cerebral ischemia or cerebral hemorrhage, leading to stroke, skin necrosis, and damage to underlying facial structures. Immediately stop the injection if a patient exhibits any of the following symptoms, including changes in vision, signs of a stroke, blanching of the skin, or unusual pain during or shortly after the procedure. Patients should receive prompt medical attention and possibly evaluation by an appropriate health care practitioner specialist should an intravascular injection occur.

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-evident 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 effectiveness 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 five years has not been established.
- In order to minimize the risks of potential complications, this product should only be used by health care practitioners who have appropriate training, experience, and who are knowledgeable about the anatomy at and around the site

of injection.

- Health care practitioners are encouraged to discuss all potential risks of soft tissue injection with their patients prior to treatment and ensure that patients are aware of signs and symptoms of potential complications.
- 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 844-235- 5234. Outside of 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

Nasolabial Fold and Acne Scar Indications:

A total of 1,542 patients have been treated with Bellafill in four U.S. clinical studies. Three of the four studies were conducted on 1,399 patients treated with Bellafill in support of the indication for the correction of Nasolabial Folds. One of the four studies was conducted on 143 patients treated with Bellafill in support of the indication for the correction of moderate to severe, atrophic, distensible facial acne scars on the cheek in patients over the age of 21 years.

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

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	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 crossover 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 the 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 U.S. 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 U.S. 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 crossover (n=46) Bellafill subjects (i.e., 97 + 46 = 143 total) compared to the 50 subjects who were initially enrolled in the Control treatment arm.

1. ***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 notedfollowing 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%)

* 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 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%)

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

2. 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 with 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.

Fourteen (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 **Table 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	**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

c) US 5-Year Post Approval Study (PAS001-Study P521-01)

In agreement with FDA, Suneva Medical conducted a 5-year prospective study of Bellafill as an injectable implant for the correction of nasolabial folds (NLF).

The primary objectives were to determine the incidence of granuloma formation and the incidence of adverse events at each follow-up period. The secondary objective was to determine the subject's assessment of satisfaction using a five-point scale at each follow-up visit over the 5 year time period.

This was a multi-center (23 sites), open-label study in which one thousand and eight (1008) subjects were followed for a five-year period after their completion of NLF correction with Bellafill. Treatments were administered according to the approved labeling for the Bellafill NLF indication. Subjects underwent up to three injection sessions over 6 weeks as needed to obtain the best possible correction.

Follow-up for AEs and satisfaction data was completed by mail or telephone questionnaire survey at 6, 12, and 18 months, and 2, 3 and 4 years post-treatment. Subjects were seen and examined in person at the 5 year post-treatment visit. If the questionnaire responses submitted at any timepoint indicated a potential adverse event in the treatment area and/or the face, the subjects were asked to return to the study site for evaluation.

Adverse events reported by subjects were confirmed and adjudicated by the investigators. Any event that an Investigator thought might potentially be a granulomatous lesion was biopsied and sent to an independent pathology lab for evaluation and diagnosis.

Primary Endpoints (safety): (1) Incidence of clinically identified and histologically confirmed granulomas tabulated by event and by subject; (2) incidence of serious unanticipated AEs stratified by severity and relation to treatment and tabulated by event and by subject; (3) incidence of anticipated AEs categorized as granulomas, serious unanticipated AEs, and AEs tabulated by event and within each study period.

Results confirmed both the short and long term (5 year) safety of Bellafill, as no device-related serious adverse events (SAEs) or unanticipated AEs were noted and the general adverse event profile was similar to prior NLF studies.

A total of 887 AEs were reported among 416 of the 1008 treated subjects. A total of 101 SAEs were reported among 75 treated subjects; none of these SAEs were considered device-related, and all were unanticipated. Of these 101 serious adverse events the majority were moderate to severe (86). The most commonly reported SAEs were “other systemic complications (46)” and “other local complications (43)” non device–related SAEs.

A total of 177 device-related AEs among 118 treated subjects were observed. Of the 177 treatment-related adverse events, the majority (131, 74%) were mild in severity. Forty-two (24%) of these related events were moderate in severity and four (2.0%) were considered severe. The most commonly reported device related adverse events were “lumpiness at the injection site” (29%) followed by “redness” (11%) see **Table 7**.

The duration of device related adverse events is provided in **Table 8**. Most of the device related adverse events were resolved during the study period. Thirty two related adverse events (18%) were deemed to be ongoing. The number of device related adverse events observed within the first month, 1-6 months, and beyond 6 months were comparable. The most common ongoing device related event was “lumpiness at the injection site” (12, 7%).

TABLE 7: Summary of Device-Related Adverse Event Severity (N=1008)

AE Category	Device-Related AE Severity			Total
	Mild	Moderate	Severe	
Lumpiness at injection site	46	6	0	52
Redness	19	1	0	20
Other local complications	13	5	0	18
Granuloma or enlargement of the implant	7	9	2	18[1]
Swelling	8	8	1	17
Pain/ Tenderness	10	4	0	14
Skin blanching or discoloration at injection site	6	3	0	9
Increased sensitivity	8	0	0	8
Itching and/or burning	7	0	0	7
Other systemic complications	0	4	0	4
Hardness at the injection area	1	1	1	3
Rash	2	0	0	2
Scab and/or Scar	0	1	0	1
Recurrence of pre-existing Herpes labialis	1	0	0	1
Tingling, numbness, temp pain in various areas of the body	1	0	0	1
Stinging	1	0	0	1
Small veins in the implant area	1	0	0	1
Total	131	42	4	177

[1]These 18 events occurred in 17 subjects. One subject had bilateral, biopsy-proven granuloma

Table 8: Summary of Device-Related Adverse Event by Duration

AE Category	Device-Related AE by Duration					Total
	≤ 30 days	31-180 days	>180 days	On Going	Missing[1]	
Other systemic complications	2	0	1	1	0	4
Other local complications	5	5	3	4	1	18
Lumpiness at injection site	8	11	19	12	2	52
Redness	7	6	6	1	0	20
Swelling	12	2	2	1	0	17
Granuloma or enlargement of the implant	0	3	5	10	0	18[2]
Pain/ Tenderness	6	2	6	0	0	14
Itching and/or burning	2	2	2	1	0	7
Increased sensitivity	1	2	5	0	0	8
Skin blanching or discoloration at injection	5	2	1	1	0	9
Rash	1	0	1	0	0	2
Hardness at the injection area	0	1	1	1	0	3
Scab and/or Scar	0	1	0	0	0	1
Recurrence of pre-existing Herpes labialis	1	0	0	0	0	1

Tingling, numbness, temp pain in various areas of the body	1	0	0	0	0	1
Stinging	1	0	0	0	0	1
Small veins in the implant area	0	0	1	0	0	1
Total	52	37	53	32	3	177

[1] AEs with missing durations.
[2] These 18 events occurred in 17 subjects. One subject had bilateral, biopsy-provengranuloma

Granulomas were encountered in 17 of 1008 subjects (1.69%). All of these cases were considered at least possibly related to the treatment; however, none were identified as SAEs. The majority of these cases were assessed as mild or moderate in severity by the investigator (15/17) and typically responded to medical therapy. Eight of seventeen (8/17) cases resolved during the course of the study, 8/17 showed improvement by study exit and were still being treated at the time of study exit, and a single lesion remaining stable at study exit, although improved from the time of diagnosis (See **Table 9**).

TABLE 9: The Time to Onset and Duration of Granuloma Formation in Bellafill Patients (N=1008)

Months from Last Treatment to Onset Date	Duration (Months)	Status at Study Exit
5	Ongoing	No change (stable)
10	3	Resolved
11	9	Resolved
12	3	Resolved
21	8	Resolved
22	4	Resolved
28	Ongoing	Improved
29	Ongoing	Improved
35	Ongoing	Improved
35	21	Resolved
35	16	Resolved
37	Ongoing	Improved
39	Ongoing	Improved
41	18	Resolved
42	Ongoing	Improved
57	Ongoing	Improved
61	Ongoing	Improved

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 have been 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 compresses, 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 the 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 10**.

Table 10: 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 fold. 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 11** and **12**, respectively.

Table 11: Mean Number of Treatment Sessions per Product

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

Table 12: 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. Approximately 80% (126/157) of 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 effectiveness 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 13)** is a four-point, static scale, ranging from minimal to severe, that relies on the depth of individual scars for severity assessment.

Table 13: Acne Scar Rating Scale (ASRS)

Score	Description
1	**Minimal –** Depth up to 0.5mm. Visibility = Perceptible with tangential lighting
2	**Mild –** Depth >0.5mm to <1.5mm. Visibility = Moderately detectable with tangential lighting
3	**Moderate –** Depth = ≥1.5mm to <2.5mm. Visibility = Easily seen with tangential lighting
4	**Severe –** Depth = ≥2.5mm in depth. Visibility = Substantial shadowing with tangential lighting

Subject and Baseline Characteristics are presented in **Table 14**.

Table 14: 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 15**. 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 (mean value shown below) with a median Acne Scar Rating Scale (ASRS) severity of 3.2 in each group.

Table 15: Acne Scar Characteristics at Baseline

Number and Severity of Scars		Bellafill (n=97)	Control (n=50)
Number of qualified	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.

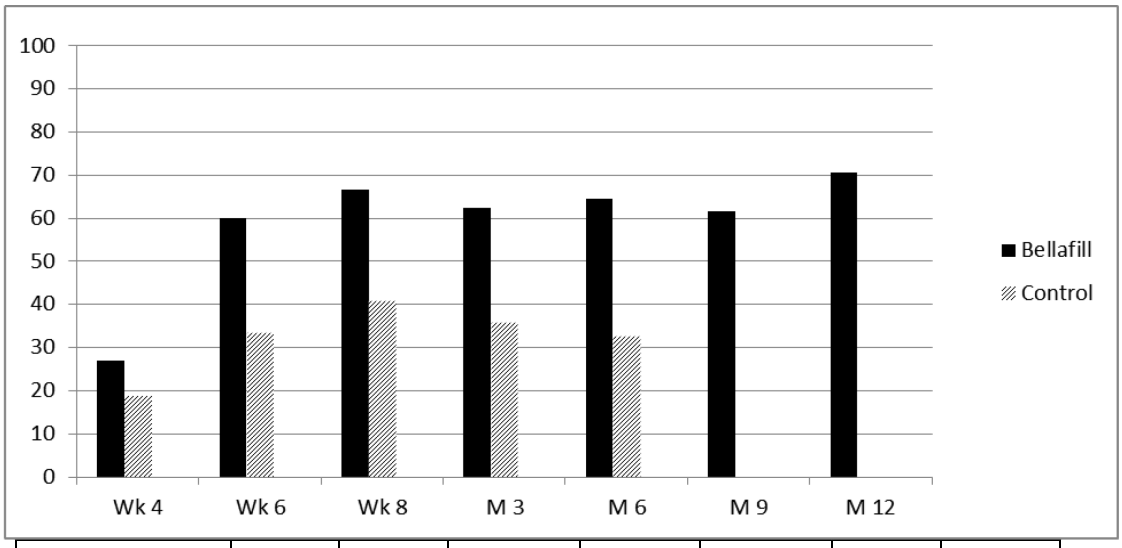
Results

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 Effectiveness 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 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 Month 6 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.) US 5-Year Post Approval Study (PAS001-Study P521-01)

Total number of Enrolled Study Sites and Subjects, Follow-up Rate: This was an open label uncontrolled study in which 23 sites enrolled 1008 subjects with a completion rate of 87% at the end of the 5-year study. The primary objectives were to determine the incidence of granuloma formation and the incidence of adverse events at each follow-up period. The secondary objective was to determine the subject's assessment of satisfaction using a five-point scale at each follow-up visit over the 5 year time period."

The Effectiveness Endpoint was based on*:* Subject satisfaction using a 5-point scale, where 1 = very satisfied, 2 = satisfied, 3 = somewhat satisfied, 4 = dissatisfied and 5 = very dissatisfied.

Study Visits and Length of Follow-up: After treatment, subsequent follow-up was conducted by mail or telephone questionnaire survey at 6, 12, and 18 months, and 2, 3 and 4 years post- treatment. Subjects were seen and examined in person at 5 years post-treatment visit.

The study population is shown in **Table 16** below. The population enrolled is typical of individuals seeking correction of NLFs in current clinical practice.

Table 16: Demographic Summary

CHARACTERISTIC	N (%) N=1008
GENDER	
Male	112 (11.1%)
Female	896 (88.9%)
ETHNICITY	
Hispanic or Latino	138 (13.7%)
Not Hispanic or Latino	870 (86.3%)
RACE[1]	
White	886 (87.9%)
Black	54 (5.4%)
Asian	12 (1.2%)
American Indian/Native Alaskan	11 (1.1%)
Native Hawaiian/Pacific Islander	2 (0.2%)
Other[2]	54 (5.4%)
AGE (yrs.)	
Mean	53.76
Range	22–86

[1] Subjects were permitted to report more than one race, therefore the total number of subjects exceeds the number of subjects in the study (N=1008).
[2] 'Other' race responses include the following:
Argentinian, Black / Korean, Hispanic or Latino, Hispanic- Portuguese, Indian, Iranian, Latino, Mexican, Mexican American, Portuguese, Puerto Rican, Spanish (Spain)

3. Results: *Effectiveness – Subject Satisfaction*

Based on subject assessment of satisfaction (using an unbalanced and unvalidated scale), patients reported satisfaction with Bellafill treatment throughout the entire study. One year after the final treatment the mean subject satisfaction rating was 1.80 (where 1= very satisfied and 2= satisfied). At 5 years after the last treatment 83% of subjects were either very satisfied or satisfied with their treatment outcome and the mean Satisfaction score was 1.70.

e) 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 crossover 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.

5-Year Post Approval Study: 1211 subjects received the Bellafill Skin Test. Eight subjects (0.7%) 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 evident 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 and 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 844-235-5234. Outside of 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 844-235-5234. Outside of 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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