A Single-Center Trial to Evaluate the Efficacy and Tolerability of the SkinPen [redacted]

[redacted]

SPONSOR STUDY NUMBER: Bellmed002

SPONSOR: Bellus Medical
[redacted]

SPONSOR'S REPRESENTATIVE:
[redacted]

TESTING AND ADMINISTRATIVE FACILITY:
[redacted]

INVESTIGATOR:
[redacted]

SUB-INVESTIGATOR/STUDY PHYSICIAN:
[redacted]

SUB-INVESTIGATOR:
[redacted]

[redacted]

[redacted] DATE:

A Single-Center Trial to Evaluate the Efficacy and Tolerability of the Skin-Pen [redacted]

SIGNATURE PAGE

[redacted]
Investigator

[redacted]
Sub-Investigator/Study Physician

[redacted]
Sub-Investigator

[redacted]
Sub-Investigator

Sponsor Representative
Bellus Medical

Date

A Single-Center Trial to Evaluate the Efficacy and Tolerability of the SkinPen [redacted]

SIGNATURE PAGE

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[redacted]

Date

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[redacted]

Date

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[redacted]

Date

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[redacted]

Date

[redacted]

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2. PURPOSE

This single-center, clinical trial is being conducted over the course of 90 days [redacted] post-treatment visits in order to assess the efficacy and tolerability of the Sponsor's SkinPen device when used by men and women with [redacted]

3. HYPOTHESIS

The Sponsor's test materials will produce a statistically significant improvement in [redacted] appearance over the course of 90 days of use (4 monthly treatments), [redacted]

4. STUDY ENDPOINTS

4.1. Primary Endpoints

- Assessment of [redacted] wrinkles severity using a [redacted] Lemperle Wrinkle Assessment Scale [redacted] 3-month post-treatment.
- [redacted]
- Monitoring of adverse events throughout the course of the study.
- Subjects global aesthetic improvement assessment at [redacted]
- Patient Satisfaction Questionnaire [redacted]
- Measurements to assess skin thickness, skin density and firmness using the OCT, ultrasound and BTC 2000 respectively. [redacted]

5. TEST MATERIAL INFORMATION

[redacted]

5.2. Characterization and Stability

The Sponsor assumes responsibility for chemical characterization and stability of the study device(s).

5.3. Study Device Description(s)

[redacted]

[redacted]

5.4. Method of Treatment Assignment

Subjects will be numbered sequentially in the order in which they qualify for entry into the study. Prior to the start of the study, all subjects will receive treatment with the device as outlined in the instructions.

5.5. Study Device Accountability

Upon receipt of the clinical supplies at the site, designated study personnel will conduct a complete inventory of all study devices and assume responsibility for their storage and dispensation.

All supplies sent to the study site will be accounted for and in no case will be used [redacted] Used and unused devices will be returned to the Sponsor. Documentation will be provided for any devices not returned by subjects in the study file.

5.6. Storage of Study Devices

The Investigator will agree to keep all study devices in a safe and secure area with restricted access in accordance with applicable regulatory requirement(s).

5.7. Treatment Compliance

Any suspected non-compliance will be addressed by the Investigator or designee. The Investigator will make a determination if a subject's non-compliance will have an effect the outcome of the study and if the subject should be dropped from the study and/or data should be excluded from statistical analyses.

6. SUBJECT ENROLLMENT AND INSTRUCTIONS

6.1. Number of Subjects

At least 33 subjects meeting the eligibility requirements are expected to complete participation in the clinical trial.

6.1.1. Determination of Sample Size

The sample size determination of this study [redacted]

6.2. Informed Consent Form

An IRB-approved informed consent form (ICF), [redacted] will be given to each candidate subject before participation in any study procedures. The candidate subject will be given as much time as needed to read the ICF and will have the opportunity to have any study related questions answered to their satisfaction prior to signing the ICF. [redacted]

6.3. Subject Identification

Subjects will be assigned a 3-digit number which, [redacted] This number will remain with [redacted]

6.4. Eligibility Criteria

Individuals will be admitted to the study at the discretion of the Investigator or designee, based on medical history and findings of the pre-study interview and examination. Individuals will be screened for the eligibility criteria listed below prior to study enrollment.

6.4.1. Inclusion Criteria

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.5. Subject Instructions

Subjects will be provided with the following instructions to follow during the study:

[redacted]

[redacted]

- To keep skincare product consistency, Subjects will be offered [redacted] Sunscreen is recommended to be applied each morning and prior to any sun exposure.

6.5.3. Subject Instructions for Study Visits

- Remove all makeup at least 30 minutes prior to each scheduled clinic visit using the provided facewash. [redacted]

6.5.4. General Study Instructions

- Avoid extended periods of sun exposure and all use of tanning beds for the duration of the study. Extra care should be taken to wear protective clothing, including sunglasses, and avoid sun exposure from 10 AM to 4 PM.
- [redacted]

7. STUDY DESIGN

7.1. Description

This is a study to evaluate the efficacy of the microneedling device in improving [redacted] Overall assessment of clinical outcome and safety will be based on clinic visits and evaluation of pre- and post- procedural photos. These photos will be [redacted] and subjects will be adequately informed of such. In conjunction with standard and close-up photography, [redacted] high-resolution ultrasonography, optical coherence tomography, transepidermal water loss measurements, and/or

BTC 2000 measurements. [redacted]

[redacted]

[redacted]

7.2. Outline of Procedures

Procedures/Time Points:	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
ICF, and qualification/enrollment paperwork	[redacted]						
Urine pregnancy test							
[redacted]							
Clinician's Global Aesthetic Improvement Assessment							
[redacted]							
[redacted]							
Imaging Procedures [b]							
[redacted]							
Patient Satisfaction Questionnaires							

7.3.

[redacted]

8. CONDUCT OF STUDY

8.1. Pre-Study Procedures

1. Prior to the start of the study, prospective subjects will be screened for eligibility requirements by telephone.

2. Prospective subjects will be informed of the pre-study washout phase pre-visit procedures as described in sections 5.5.1 and 5.5.3.

3. Prospective subjects will be assigned an appointment time for visiting the clinic.

8.2. Baseline: Visit 1 (-14 to 0 day[s])

1. Candidate subjects will be given an IRB-approved informed consent form (ICF) [redacted]
2. Candidate subjects will complete an eligibility and health questionnaire.
3. Candidate subjects that sign the initial paperwork will be assigned a screening number.
4. Candidate subjects will be screened by the Investigator or designee for qualification criteria.
5. Candidate subjects that pass the initial screening will be graded for wrinkle severity and as described in section 8.1.
6. Those that pass eligibility requirements and are female will perform a pregnancy test (if necessary); if the test is negative or the candidate subject is male, the subject will be enrolled into the study and assigned a subject number.

[redacted]

8.3. Interim Visits: Visits 2-5 [redacted]

- A clinician will record concomitant medications and will ask subjects if they have experienced any changes in their health since the previous visit. [redacted]
- [redacted]

3. After acclimation, subjects will participate in TEWL Measurements, OCT images, high frequency ultrasounds images, BTC images and imaging procedures as described in section [redacted]

[redacted]

5. Trained aestheticians will treat [redacted]
6. Subjects will be provided with supporting materials, usage instructions and a daily diary. New diaries will be distributed at Visit [redacted]

8.4. Post-Treatment Visit: Visit 6 [redacted]

- A clinician will record concomitant medications and will ask subjects if they have experienced any changes in their health since the previous visit. [redacted]

[redacted]

2. Supporting products and daily diary distributed at Visit [redacted] will be reviewed for compliance. [redacted]

3. After a 15 minute acclimation to ambient temperature and humidity conditions, subjects will participate in the following procedures:
   - Imaging procedures as described in section [redacted]
   - Assessment of Wrinkle [redacted]
   - Clinician's global aesthetic improvement assessment as described in section [redacted]
   - Subject's self-assessment on improvement as described in section [redacted]
   - Patient Satisfaction Questionnaire as described in section [redacted]
   - TEWL measurement, OCT images, high frequency ultrasound images and BTC 2000 measurement.

8.5. Post-Treatment Visit: Visit 7 [redacted]

1. A clinician will record concomitant medications and will ask subjects if they have experienced any changes in their health since the previous visit. [redacted]

2. Subjects will participate in pregnancy screening procedures.

3. After a 15 minute acclimation to ambient temperature and humidity conditions, subjects will participate in the following procedures:
   - Imaging procedures as described in section [redacted]
   - Assessment [redacted] wrinkle [redacted]
   - Clinician's global aesthetic improvement assessment as described in section [redacted]
   - Subject's global aesthetic improvement as described in section 8.2.2
   - Patient Satisfaction Questionnaire as described in section 8.6.
   - TEWL measurement, OCT images, high frequency ultrasound images and BTC 2000 measurement.

[redacted]

[redacted]

[redacted]

[redacted] ASSESSMENTS

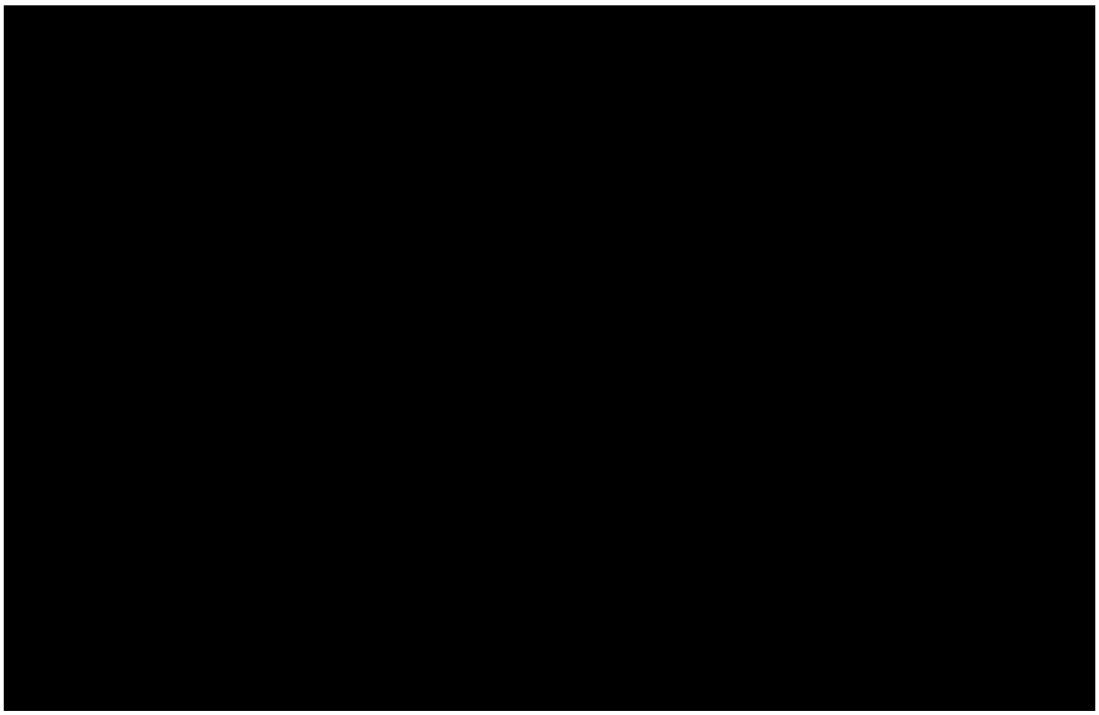
Note that the order of the assessment listed below may be altered from the order indicated in the study visits in order to help study flow, or at the recommendations of the Sponsor or Investigator. Any change in the order of procedures will not compromise study data.

9.1. Assessment [redacted] Wrinkling

Assessment of [redacted] wrinkling will be performed at [redacted] will be assessed according to the following definitions:

Class 0: No Wrinkles
Class 1: Just perceptible wrinkle
Class 2: Shallow wrinkles
Class 3: Moderately deep wrinkle
Class 4: Deep wrinkle, well-defined edges
Class 5: Very deep wrinkle, redundant fold

[redacted]



[redacted]

9.2. Global Aesthetic Improvement Assessment

8.2.1 Clinician's Global Aesthetic Improvement Scale (CGAIS)

Rating	Description
1	**Very Much Improved:** Optimal cosmetic result in this subject.
2	**Much Improved:** Marked improvement in appearance from the initial condition, but not completely optimal for this subject.
3	**Improved:** Obvious improvement in appearance from initial condition, but a re-treatment is indicated.
4	**No Change:** The appearance is essentially the same as the original condition.
5	**Worse:** The appearance is worse than the original condition.

8.2.2 Subject Global Aesthetic Improvement Scale (SGAIS)

Rating	Description
1	**Very Much Improved:** Optimal cosmetic result.
2	**Much Improved:** Marked improvement in appearance from the initial condition, but not completely optimal.

3	**Improved:** Obvious improvement in appearance from initial condition.
4	**No Change:** The appearance is essentially the same as the original condition.
5	**Worse:** The appearance is worse than the original condition.

9.3. Imaging Procedures

Prior to photography procedures, clinic personnel will ensure that subjects [redacted] neck [redacted] as described in the study procedures. Subjects will remove any jewelry from the area(s) to be photographed and equilibrate for at least 15 minutes to ambient conditions within the clinic before any photographs are taken. [redacted] Subjects will be provided with a black matte t-shirt or a black or gray matte cloth will be draped over the subjects' clothing.

[redacted]

[redacted]

9.3.2. NIKON D7100

Standard, close-up and cross-polarized photography of [redacted] neck will be utilized for evaluation of [redacted] wrinkles. These photographs will be taken utilizing the Nikon [redacted]

9.4. Noninvasive Procedures

Biox Aquaflux will be used to measure transepidermal water loss (TEWL) measurements which evaluate barrier function of the skin epidermal layer to determine progress of epidermal healing after treatment. [redacted] an Optical coherence tomography (OCT) device, will be used to noninvasively gather [redacted] images of pre- and post-treated skin. The BTC 2000 will be used to measure skin laxity, viscoelastic deformation, stiffness, energy absorption, elasticity, and deformation values of skin. [redacted]

[redacted]

9.6. Patient Satisfaction Questionnaires

Subjects will complete a Sponsor-provided self-assessment questionnaire [redacted]

10. ADVERSE EVENTS

10.1. Definition of an Adverse Event

An adverse event (AE) is any untoward medical occurrence in a clinical investigation where a subject is administered a pharmaceutical product/biologic (at any dose), OTC, cosmetic product or medical device and which does not necessarily require a causal relationship with a test article. [redacted]

10.2. Assessment of Severity and Relationship

The Investigator or medical staff will evaluate all AEs as to their severity and relation to the test article.

The severity of an AE will be graded as follows:

Mild: Awareness of a sign or symptom but easily tolerated

Moderate: Discomfort sufficient to cause interference with usual activity or to affect clinical status

Severe: Incapacitating with inability to do usual activity or to significantly affect clinical status

[redacted]

10.3. Definition of a Serious Adverse Event

A serious adverse event (SAE) is any experience or reaction occurring at any dose that results in any of the following outcomes:

- death,
- is life threatening,
- inpatient hospitalization or prolongation of hospitalization,
- a persistent or significant disability/incapacity, or
- a congenital anomaly/birth defect.

[redacted]

[redacted]

[redacted]

10.4. Procedures for Reporting Adverse Events

At each visit, the Investigator or designee will question the subject about adverse events using an open question and taking care not to influence the subject's answer (e.g. "Have you noticed any change in your health since the last visit?").

[redacted]

[redacted]

The Sponsor will be notified of all AEs within 5 business days. Photographs will be taken to document any AEs if possible.

10.5. Procedures for Reporting Serious Adverse Events

Any SAE that occurs during the study whether related to the treatment or not, expected or not, will be reported to the Sponsor Representative immediately (within 24 hours of being reported to the Investigator) [redacted]

10.6. Procedures for Reporting Pregnancies

All pregnancies occurring during clinical studies must be reported to the Sponsor by the Investigator within 24 hours of observation or notification of the occurrence. [redacted]

10.7. Medical Treatment for Adverse Events and Serious Adverse Events

[redacted]

[redacted]

[redacted]

10.9. Anticipated Reactions

Expected side effects: After the procedure, the skin will be red and flushed in appearance, similar to a moderate sunburn. The patient many also experience skin tightness and mild sensitivity to touch on certain areas. This will diminish significantly within a few hours following the procedure. Within the next 24 hours, the skin will have returned to normal. After three days, there is rarely any evidence that the procedure has taken place.

[redacted]

11. ATTRITION

Clinical studies may experience attrition. Subjects will be made aware that they are free to withdraw from the study at any time for any reason, without prejudice. Otherwise, every effort will be made to have subjects complete the study as stated in this protocol, ensuring subject safety and following the provisions of the informed consent form. [redacted]

12. ADVERSE WEATHER PROVISION

[redacted]

[redacted]

13. PROTOCOL MODIFICATIONS

Protocol amendments will be written to record any changes or formal clarification to the procedures outlined in the protocol. Any violations to the protocol that might significantly affect the completeness, accuracy and/or reliability of the study data or might affect the subjects' rights, safety or well-being will be documented as protocol deviations.

All protocol amendments will be forwarded to the IRB for review and approval prior to implementation, even if it is determined the safety of the subjects will not be affected. [redacted]

[redacted]

14. ETHICAL AND REGULATORY PROCEDURES

14.1. Research Standards/Good Clinical Practice

The conduct of this study will follow all applicable guidelines for the protection of human subjects for research as outlined in 21 CFR 50, in accordance with the accepted standards for Good Clinical Practice (GCP), International Conference on Harmonization (ICH), and the standard practices of UT Southwestern..

14.2. Quality Control and Quality Assurance

The Investigator will permit trial-related monitoring, audits, IRB review, and regulatory inspection(s) by providing direct access to source data/documents. [redacted]

14.3. Institutional Review Board

This study (protocol, ICF and all addenda) will be reviewed and approved by an Institutional Review Board (IRB). The study will not be activated, subjects will not be consented or receive any study devices or participate in any study procedures until such time as the IRB has approved the protocol and the ICF. [redacted]

15. BIOSTATISTICS AND DATA MANAGEMENT

15.1. Statistical Analysis Population

The per-protocol (PP) population will be the primary population for all statistical analyses. [redacted]

[redacted]

15.2. Statistical Analysis Plan

This initial study will include descriptive statistics and change from baseline analysis.

[redacted]

A descriptive statistical summary will be provided for all clinical assessments (including wrinkle severity using the Lemperle Wrinkle Assessment Scale, [redacted] subjects global aesthetic improvement (SGAIS), Aquaflux, Vivosight, BTC 2000 measurements [redacted]. The descriptive statistical summary includes the number of observations (N), mean, median, standard deviation (SD), minimum (MIN) and maximum (MAX) of scores/values at all applicable time points.

Mean of the change from baseline (defined as post-baseline value minus baseline value) will be estimated at post-baseline time points for applicable parameters. The null hypothesis, that the mean change from baseline is zero, will be tested using methods described in the Statistical Analysis Plan table.

The following will be calculated and reported for each evaluation parameter at the applicable post-baseline time point(s):

$$\text{Percent mean change from baseline} = \frac{\text{(visit mean score – baseline mean score) x 100}}{\text{baseline mean score}}$$

$$\text{Percent of subjects improved/worsened} = \frac{\text{(number of subjects improved/worsened from baseline) x 100}}{\text{total number of subjects}}$$

[redacted]

[redacted]

[redacted]

[redacted]

All statistical tests will be 2-sided at significance level alpha=0.05. P-values will be reported to 3 decimal places (0.000). No multiple testing corrections will be considered in the study. Statistical analyses are performed using SAS software version 9.4 or later series (SAS Statistical Institute). [redacted]

[redacted]

16. CLINICAL STUDY REPORT

A clinical study report will be drafted using template and incorporating any documented Sponsor preferences on file. The draft report will be submitted to the Sponsor for approval prior to finalization, and revisions may be made at the Sponsor's request.

[redacted]

17. MAINTENANCE OF RECORDS

Original records (including the study protocol, clinical grading records, medical histories, informed consent forms, screening/enrollment logs, and any other case report forms used in the study) and a copy of the final study report will be retained on file [redacted] or a minimum of 2 years. When the archiving time has expired, the study information will either be destroyed or sent to the Sponsor [redacted]

[redacted]