A Prospective, Multicenter, Single Arm Clinical Study Evaluating the Use of J-Plasma® for Dermal Resurfacing

Clinical Study Protocol

Study Protocol No: **VP-1558**

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Sponsor: Bovie Medical Corporation
5115 Ulmerton Road
Clearwater, FL 33760-4004 USA
Phone: (800) 537-2790
Fax: (800) 323-1640

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LIST OF ABBREVIATIONS

AE	Adverse Event
CRF	Case Report Form
CRO	Clinical Research Organization
DCF	Data Clarification Form
DRM	Data Review Meeting
ESU	Electrosurgical Generator Unit
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSS	Fitzpatrick Skin Scale
FWS	Fitzpatrick Wrinkle and Elastosis Scale
GAIS	Global Aesthetic Improvement Scale
GCP	Good Clinical Practice
ICH	International Conference for Harmonization of Technical Requirements of Pharmaceuticals for Human Use
IFU	Instructions for Use
IPR	Independent Photographic Reviewer
IRB	Institutional Review Board
ITT	Intent-to-Treat
NSAID	Non-steroidal Anti-Inflammatory Drug
PP	Per Protocol
PSR	Plasma Skin Resurfacing
PPS	Per Protocol Set
RF	Radiofrequency
SAE	Serious Adverse Event
UADE	Unanticipated Adverse Device Effect
VAS	Visual Analog Scale

1 STUDY SYNOPSIS

Study Title	A Prospective, Multicenter, Single-Arm Clinical Study Evaluating the Use of J-Plasma® for Dermal Resurfacing
Study Device	J-Plasma® system
Study Population	The study population will consist of males and females, 30 years of age or older, requesting a procedure for the purpose of improving facial appearance by reducing facial wrinkles and rhytides. Those subjects who meet eligibility criteria and agree to provide written informed consent will be invited to participate.
Study Objective	The study objective is to demonstrate the safety and efficacy of the J-Plasma® system for use in dermal skin resurfacing.
Study Design	This is a multi-center, single arm, evaluator-blind prospective study of 55 study subjects who are seeking a procedure to reduce the appearance of wrinkles and rhytides from up to 5 investigational centers in the United States. Each study subject will receive one procedure with J-Plasma® at enrollment. Follow-up will occur immediately following the procedure, at 10 days, 1, 3, and 6 months after enrollment.
Study Endpoints	**Primary Efficacy Endpoint** is the comparison of the proportion of subjects (i.e. percentage of treatment responders) with a ≥ 1-score improvement on the FWS at the 3-month visit, as compared to baseline as determined by at least 2 out of 3 blinded Independent Photographic Reviewers. The study design assumes a 75% success rate of subjects with treated wrinkles with a ≥ 1-score change on the FWS; therefore, greater than 75% of subjects must be rated with a ≥ 1-score improvement 3 months after treatment and must be statistically significantly greater than 75%. **Primary Safety Variable** is the evaluation of adverse events up to the 3-month visit after treatment. **Secondary Efficacy Endpoint:** Subjects with a ≥ 1-score improvement on the FWS and at least a self-reported "improved" rating on the modified GAIS at the 3-month visit will be considered to have an aesthetic pleasing outcome. The modified GAIS is a measure of aesthetic improvement relative to the baseline, pre-treatment condition. **Secondary Safety Variable** is the evaluation of the pain and discomfort after treatment as reported by the subject on a visual analog scale (VAS).
Additional Endpoints	• FWS ≥ 1-score improvement and ≥ 75% agreement with at least an "improved" rating by the subject on the modified GAIS. • Magnitude of improvement measured by the mean change in FWS from baseline to 3 months visit. • Subject satisfaction with procedure recorded at the 3-month visit. • Achievement of re-epithelialization by facial zone and across all facial zones at the 10 day, 1-month and 3-month follow-up visits as reported by the investigator. • Mean duration until study subject feels comfortable going in public after treatment as reported by the study subject. • Daily 10-point Visual Analog Scale (VAS) pain assessment following treatment through the 10 day follow-up visit by diary day with a change from the VAS pain score at baseline.

	• The proportion of subjects (i.e. percentage of treatment responders) with correctly identified 3-month images, in comparison to baseline, as determined by at least 2 out of 3 blinded Independent Photographic Reviewers.
Planned Study Period	Study enrollment is expected to occur over 3-6 months. Imaging and study assessments will continue through 3 months post-procedure, with long term subject follow-up and data collection through 6 months post-procedure. Total study duration is expected to be approximately 9-12 months. It is expected that the 510(k) application for the device will be submitted based on 3 month post-procedure results. However, this clinical trial will continue until every enrolled subject has reached 6 months following their procedure. At that time, the trial will be considered complete, the final results will be determined, and a final report will be prepared.

2 STUDY ADMINISTRATIVE STRUCTURE

Study Sponsor:
Bovie Medical Corporation
5115 Ulmerton Road
Clearwater, FL 33760-4004
Phone: (800)537-2790
Fax: (800)323-1640

Clinical Research Organization (CRO):
NAMSA
400 Hwy 169 South, STE 500
Minneapolis, MN 55426

Proprietary Notice:
This document contains mainly unpublished data and is the sole property of the Sponsor. Therefore, it is provided to you in strict confidence as an investigator, potential investigator, or consultant. The information may be reviewed by you, your staff, and your institutional review board. It is understood that this information will not be disclosed to others without written authorization from the study Sponsor except to the extent necessary to obtain informed consent from those persons to whom the investigational device may be implanted.

Ethics Statement:
The study will be completed in accordance with applicable regulations and standards to provide public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki.

3 INTRODUCTION

3.1 Study Background

Physiological skin aging is multi factorial and results from both intrinsic and extrinsic factors. Genetics is one example of an intrinsic factor, others include hormone and metabolic processes that can cause the skin to age. Exposure to chronic light, radiation, pollution, chemicals and toxins, are examples of extrinsic factors. Since skin health and beauty is contemplated as one of the representation of overall "well-being" and "health", several anti-aging therapies have been developed during the recent years. The goal of these therapies is to achieve a healthy, smooth, blemish-free, translucent and resilient skin. [1]

Skin resurfacing or peel procedures have become an established non-surgical method for reducing certain skin imperfections such as wrinkles, rhytides, dark spots, scars, or blemishes. Traditional fully ablative and fractional lasers are the most commonly used devices for skin resurfacing.

The skin is composed of three layers: the epidermis, the dermis, and the hypodermis. The dermis contains well-organized and oriented collagen fibers that contribute to the firmness and smoothness of the skin. As people age, these collagen fibers reduce in number and become less organized, resulting in sagging and/or wrinkled skin. When esthetic procedures are scheduled for older adults, the rate of the epidermal turnover associated with a slower wound healing and less effective desquamation (shading of outer layers of the skin), needs to be taken into consideration.[1]

In most skin resurfacing procedures, an energy source (heat, radiofrequency energy, etc.) is used to selectively damage the skin and prompt a healing response that stimulates the growth of new collagen fibers in the dermis that are well-organized. The healing response and new collagen formation results in skin that is smoother and firmer.

There are numerous traditional fully ablative and fractional lasers on the market today used for skin resurfacing. Traditional and fractional lasers differ in their method of treatment. Traditional lasers have a single beam that burns or damages all of the epidermis within the treatment area of the beam. Fractional lasers divide the beam into multiple smaller beams and treat only a "fraction" of the epidermis to affect changes in the deeper epidermis or dermis. This results in multiple small cores of laser damage surrounded by areas of healthy tissue. When compared to traditional lasers, fractional lasers deliver a more superficial treatment resulting in less risk for complications and reduced time for healing. However, this also means more treatments may be required to achieve the desired results especially in areas of deep lines or wrinkles. Healing times vary by amount of treatment, but fractional laser recovery time is typically one week compared to three to four weeks for traditional lasers.

In the wake of the demonstrated safety and efficacy of laser skin resurfacing, multiple additional treatment modalities have been developed for this application including the use of radiofrequency (RF) energy. The fractionated radiofrequency results in epidermal and subepidermal ablation under the conductive pins that reproduces similar effects as a fractional CO_2 laser with dermal heating, seen in the non-ablative lasers and devices.[2] The combination of epidermal ablation and dermal heating with radiofrequency, called sublative resurfacing in some studies, is suitable for skin types I–IV, for the treatment of skin laxity, wrinkles, enlarged

pores, pigmented lesions, acne, telangiectasias, and scarring from trauma or acne. Subject recovery and down time periods are significantly lower when compared with ablative laser healing times, with minimal adverse effects.[3]

3.2 Study Rationale

An emerging method utilizing the state of matter known as plasma to create a thermal effect on the skin through the use of positively ionized gasses is plasma skin resurfacing (PSR).[4] As this plasma comes in contact with the resurfacing target, the positive ions capture back electrons while energy is released. With PSR, an inert gaseous source is used to form a plasma that releases thermal energy that eliminates oxygen from the targeted skin surface. [5,6] PSR is not dependent on a chromophore for its use and does not vaporize tissue as ablative lasers do. This resurfacing modality has been hypothesized to function by forming a layer of desiccated epidermis creating a natural barrier that facilitates accelerated healing with generation of new epidermis. PSR also penetrates to the upper dermis resulting in thermal denaturation of surrounding collagen, thereby increasing fibroblast activity, which has been shown to continue up to a year after the plasma treatments. [7] Plasma resurfacing has been safely used in Fitzpatrick skin types I–IV. It has been approved for the treatment of many skin conditions including photoaging, acne scars, rhytides, dyschromias, skin laxity, as well as the treatment of actinic keratosis and seborrheic keratosis. In contrast to the ablative laser, plasma resurfacing treatments have a very low incidence of side effects such as permanent hypopigmentation, scarring, or prolonged erythema. [8]

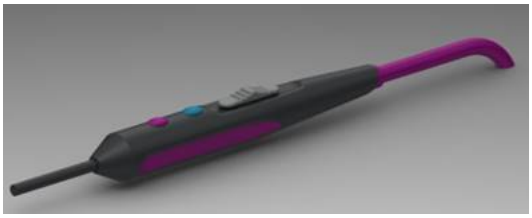
As an alternative treatment modality for skin resurfacing, Bovie Medical Corporation has developed the J-Plasma® system that delivers RF energy in a controlled fashion with similar depth of thermal effect as predicate devices currently on the market for dermal resurfacing and wrinkle reduction procedures. [9,10,11] A potential benefit of this single-treatment low-risk technology is reducing wrinkle appearance and enhancing well-being by improving satisfaction and perception of having a more youthful appearance.

3.3 Study Device Description

The J-Plasma® system consists of an electrosurgical generator unit (ESU, Figure 1), a handpiece (Figure 2), and a supply of helium gas. RF energy is delivered to the handpiece by the ESU and used to energize an electrode. When helium gas is passed over the energized electrode, a helium plasma is generated which allows for conduction of the RF energy from the electrode to the subject in the form of a precise helium plasma beam.

Figure 1: Electrosurgical generator unit

Figure 2: Handpiece



Bovie Medical Corporation's J-Plasma® helium-based plasma technology has received FDA clearance (K112233, K151325, K152570, and K170188) for the cutting, coagulation, and ablation of soft tissue.

Pre-clinical studies comparing J-Plasma® to other energy sources such as CO_2 laser and RF energy demonstrated less or comparable lateral and depth of thermal spread for J-Plasma® in porcine peritoneum, bladder, and small intestine[12].

Additionally, a pre-clinical study comparing J-Plasma® to the Rhytec Portrait PSR for ablation of porcine dermis was conducted to evaluate performance the J-Plasma®. Four animals were utilized in the study to evaluate both devices at acute and chronic time points. At the acute time point, J-Plasma using 1 pass at both 20% and 40% power was very similar to the results observed with the Rhytec system at PSR2 and PSR3 settings. At the chronic time point, dermal changes with the J-Plasma® appeared to extend deeper into the dermis than that observed with the Rhytec treated tissue, which may be beneficial and possibly demonstrate superior performance. These results support the safety of J-Plasma® for this application and equivalent tissue effects for the two technologies.

These pre-clinical study results demonstrate safety and efficacy of the J-Plasma® system in the ablation of soft tissue within its current FDA cleared indications in an animal model, therefore making the J-Plasma® system a viable technology for dermal skin resurfacing.

4 STUDY DESIGN

4.1 Study Objective

The study objective is to demonstrate the safety and efficacy of the J-Plasma® system for use in dermal skin resurfacing.

4.2 Study Design

This is a multi-center, single arm, evaluator-blind prospective study of 55 study subjects who are seeking a procedure to reduce the appearance of wrinkles and rhytides at up to 5 investigational centers in the United States.

Study subjects that meet study eligibility criteria and have provided informed consent will be enrolled in the study. During the procedure, the investigators will use J-Plasma® on applicable facial zones to reduce wrinkles and rhytides.

Study subjects will be followed immediately following the procedure, at 10 days, 1, 3, and 6 months post-procedure for study assessments.

Study enrollment is expected to occur over 3-6 months. Imaging and study assessments will continue through 6 months post-procedure. Total study duration is expected to be approximately 9-12 months. It is expected that the 510(k) application for the device will be submitted based on 3 month post-procedure results. However, this clinical trial will continue until every enrolled subject has reached 6 months following their procedure. At that time, the trial will be considered complete, the final results will be determined, and a final report will be prepared.

4.3 Study Endpoints

The following endpoints will be assessed in this study.

4.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the comparison of the proportion of subjects (i.e. percentage of treatment responders) with a ≥ 1-score improvement on the FWS at the 3-month visit, as compared to baseline as determined by at least 2 out of 3 blinded Independent Photographic Reviewers. The study design assumes a 75% success rate of subjects with treated wrinkles with a ≥ 1-score change on the FWS; therefore, greater than 75% of subjects must be rated with a ≥ 1-score improvement 3 months after treatment and must be statistically significantly greater than 75%.

4.3.2 Primary Safety Variable

The primary safety variable is the evaluation of adverse events up to the 3-month visit after treatment.

4.3.3 Secondary Efficacy Endpoint

Subjects with a ≥ 1-score improvement on the FWS and at least a self-reported "improved" rating on the modified GAIS at the 3-month visit will be considered to have

an aesthetic pleasing outcome. The modified GAIS is a measure of aesthetic improvement relative to the baseline, pre-treatment condition.

4.3.4 Secondary Safety Variable

The secondary safety variable is the evaluation of the pain and discomfort after treatment as reported by the subject on a visual analog scale (VAS).

4.3.5 Additional Endpoints

Other endpoints to be evaluated include:

1. FWS ≥ 1-score improvement and ≥ 75% agreement with at least an "improved" rating by the subject on the modified GAIS. The modified GAIS is a measure of aesthetic improvement relative to the baseline, pre-treatment condition.
2. Magnitude of improvement measured by the mean change in FWS from baseline to 3 months visit.
3. Subject satisfaction with procedure recorded at the 3-month visit.
4. Achievement of re-epithelialization by facial zone and across all facial zones at the 10 day, 1-month and 3-month follow-up visits as reported by the investigator.
5. Mean duration until study subject feels comfortable going in public after treatment as reported by the study subject.
6. Daily 10-point Visual Analog Scale (VAS) pain assessment following treatment through the 10 day follow-up visit by diary day with a change from the VAS pain score at baseline.
7. The proportion of subjects (i.e. percentage of treatment responders) with correct identification of 3-month images, in comparison to baseline, as determined by at least 2 out of 3 blinded Independent Photographic Reviewers.

4.3.6 Subgroup Analysis

Subgroup analyses will include stratifying the primary endpoint, (percent treatment responders on FWS), on age, gender, race/ethnicity, and Fitzpatrick Skin Scale (FSS). Additionally, the degree of improvement on FWS (e.g. 2, 3 or 4-score improvement) will be reported.

5 INVESTIGATORS SELECTION AND STUDY POPULATION

5.1 Investigator Selection

Participating Investigators will be qualified based on professionals experienced in treatment of wrinkles, such as dermatologists or plastic surgeons. Investigators will be selected based on interest and availability for participation in the study; ability to provide qualified subjects; adequate support staff; experience conducting clinical research; and willingness to comply with the protocol, IRB requirements, regulatory requirements (including the signed investigator agreement and statements disclosing any financial relationship investigators might have with Bovie Medical Corporation), and FDA regulations.

5.2 Study Population

All subjects requesting a procedure for the purpose of improving facial appearance by reducing facial wrinkles and rhytides from each participating investigator's subject population will be considered as candidates for the study. Those subjects who meet eligibility criteria and agree to provide written informed consent will be invited to participate.

Subjects will be considered enrolled into the study when they have signed an approved informed consent form, meet all study criteria, and have undergone a procedure with the J-Plasma system.

5.2.1 Inclusion Criteria

Potential subjects must meet all of the following inclusion criteria:

1. Male or female subjects ≥30 years of age.
2. Subject is seeking improvement of facial appearance by reducing facial wrinkles and rhytides.
3. Subject with a facial wrinkle score rating of at least 2 on the FWS as determined by the investigator.
4. Subject with a Fitzpatrick Skin Scale score ≤III.
5. Subject is willing and able to provide written informed consent.
6. Subject is willing and able to comply with protocol requirements, including obtaining study-required images/photos and assessments, and returning for follow-up visits.
7. Subject is willing to release rights to study Sponsor for the use of the photos, including in potential publication.
8. Subject is willing to abstain from other facial cosmetic procedures through the 6 month follow-up visit; examples include, but are not limited to, laser or chemical re-surfacing, dermabrasion, neuromodulator and/or filler injections, aesthetic facial surgery, etc.

5.2.2 Exclusion Criteria

Subjects will be excluded from the study if they meet any of the following criteria:

1. Subject with a Fitzpatrick Skin Scale score >III.
2. Subject is pregnant or lactating.
3. Active HSV-1 or diabetes mellitus.
4. Active cut, wound, or infection on the skin of the face.
5. Subject has used, within the past 30 days, Accutane or any medication that can cause dermal hypersensitivity.
6. Subject has a history of autoimmune disease.
7. Subject with a bleeding disorder or who is on blood thinning medication that may be at risk for bleeding.
8. Subject has a known adverse reaction to anesthetics.
9. Subjects with active skin disease of the facial area or known connective tissue disease.
10. Subjects with known susceptibility to keloid formation or hypertrophic scarring.
11. Subjects with present cancerous or pre-cancerous lesions in the area to be treated.
12. Subject who, for any reason, suspects that they will not be able to complete the prescribed follow-up assessment(s);
13. Subject has had concurrent therapy that, in the investigator's opinion, would interfere with the evaluation of the safety and efficacy of the study treatment method.
14. Subject is not willing to release rights to study Sponsor for the use of the photos, including in potential publication.
15. Subject is enrolled in another investigational (drug or device) clinical trial that can interfere with this study's assessments.
16. Subject has undergone a facelift procedure or received facial injections within the past year.

6 STUDY PROCEDURES

6.1 Informed Consent

The Investigator must ensure that written informed consent to participate in the study and written authorization for use and disclosure of protected health information is obtained before including any individual as a subject in the study, and before conducting any study-related assessments. The Investigator must provide the prospective subject with sufficient opportunity to consider whether or not to participate, and minimize the possibility of coercion or undue influence.

To participate in the study, a subject must sign and date an IRB-approved consent document. The original, signed documents will be kept with the subjects' files and copies will be provided to the subjects. The informed consent process must be followed, and the subject's participation in the study, must be documented in the subject's medical record/chart.

6.2 Pre-Procedure

The subjects will have verification of eligibility criteria, a brief general examination including medical history, and wrinkles/rhytides assessment completed within 21 days prior to undergoing the study procedure. Up to two urine pregnancy tests must be obtained prior to study procedure for females with child-bearing potential (one at pre-procedure screening and one on the day of the procedure prior to the procedure if pre-procedure screening and procedure are not performed on the same day).

Additionally, photographs of the area to be treated with the study device will be taken using the Canfield Scientific Visia-CR 2.3 system (see also Section 12.3 Data Management Responsibilities and Section 12.3 Data Capture Methods) for each subject to document the appearance of their facial wrinkles and rhytides. The same standardized photography views will be used throughout the study as documented in the Canfield User Manual document developed for the study.

The study subjects may be given medication for the prophylactic treatment of bacterial and viral infections including herpes simplex based on investigator's discretion.

Medications subject is taking upon entry into the study should also be documented in the Case Report Forms (CRF). Documentation should include medications that study subjects take on an elective basis in addition to prescribed medications. Medication used for analgesia and/or anesthesia should be recorded as concomitant medication as well. To ensure the capture of the foregoing information on pre-existing conditions, sites should also be attentive to the need to document without limitation and whenever discovered: (1) all chronic, episodic or 'as needed' medications used before study enrollment; (2) prior episodic or 'as needed' therapeutic interventions, procedures or hospitalizations; and, (3) recent or planned surgical procedures.

6.3 Study Procedure

On the day of the procedure and prior to the study procedure, female subjects with child-bearing potential must complete a urine pregnancy test (result must be obtained prior to the procedure).

Additionally, subjects must complete a VAS pain assessment pre-procedure and immediately following the procedure.

During the study procedure, the face of each subject will be treated by the study investigator using J-Plasma® according to the IFU and procedures described in this section. The face will be divided into 5 zones: Zone 1 (perioral), Zone 2 (periorbital), Zone 3 (forehead), Zone 4 (nose), and Zone 5 (cheeks). Tumescent (an anesthetic) will be injected under the subject's skin. The volume of tumescent used in each Zone will be based on the investigator's discretion and will be documented in the CRFs. The plasma beam will be used to ablate the tissue in each Zone using slow, but steady movement of the beam. All Zones will be treated with only a single pass of the plasma beam. Special care must be taken to not pass over any treated area more than once. Zone 1 (perioral) and Zone 2 (periorbital) will be treated with a maximum of 20% power and 4 liters/minute helium flow. Zones 3, 4, and 5 (forehead, nose, and cheeks, respectively) will be treated with a maximum of 40% power and 4 liters/minute of helium flow. The ablated tissue will not be wiped away.

6.4 Follow-up Procedures

Following the procedure, the research staff and the subject will care for the treated areas using the Post-Procedure Care Guidelines listed below:

Post-Procedure Care Guidelines

Days 0-10:

- Keep skin moist at all times, use of a cool mist vaporizer on face as much as possible is recommended
- Keep skin covered with a generous layer of petroleum jelly (i.e., Vaseline Petroleum Jelly) at all times
- Perform cool water soaks every 1-2 hours as tolerated on days 0-2, then every 2-4 hours on days 3-10
  - Fill a clean bowl with cold tap water and a few ice cubes and 1 tablespoon of white vinegar for every cup of water
  - Using clean 4x4 gauze pads, wet them with the water solution and apply over the face, replacing them with new wet gauzes before they dry; alternatively, cold water may be repeatedly dripped over the gauze
  - Continue soak for approximately 30 minutes
- After soak is over, pat dry with a clean, soft towel and reapply petroleum jelly

Days 11 and beyond:

- Apply light moisturizer and sun protection as directed by the investigator

Following the study procedure, subjects will be asked to complete VAS pain assessment and return to the study site at 10 days (9-14 days), 1 month (23-37 days), 3 months (80-100 days), and 6 months (166-194 days) for post-procedure assessments and to complete questionnaires or answer questions asked by study staff. Additionally, photographs of the treated areas will be taken using the Canfield Scientific Visia-CR 2.3 system (see also Section 12.3 Data Management Responsibilities and Section 12.3 Data Capture Methods) for each subject to document the appearance of their facial wrinkles and rhytides. Study subjects will also be asked

to report complications experienced post-procedure and complete daily VAS 0-10 scale pain assessments utilizing the Subject Diary (see Appendix C: Subject Diary), and date when study subject felt comfortable, willing and able to go in public following the procedure. Table 1 illustrates study procedures that will occur at each visit.

Table 1: Study Required Procedures

	Baseline/ Pre-Procedure Screening[1]	**Procedure**	**10 Days**	**1 mo**	**3 mo**	**6 mo**
			10+4/-1 days	30±7 days	90±10 days	180±14 days
Informed Consent	√					
Assess Inclusion/Exclusion Criteria	√					
Urine Pregnancy Test[2]	√	√				
Medical History	√					
General Physical Exam	√					
Review Medications	√		√	√	√	√
Photographic Images[3]	√		√	√	√	√
Fitzpatrick Skin Scale (FSS)	√					
Fitzpatrick Wrinkle and Elastosis Scale (FWS) [4]	√		√	√	√	√
Visual Analog Scale (10-point VAS) [5]		√	√	√	√	√
Study Procedure		√				
Subject Diary (10-point VAS)[6]		√	√			
Adverse Event Assessment		√	√	√	√	√
Re-epithelization and Down Time[7]			√	√	√	
Modified Global Aesthetic Improvement Scale (GAIS) [8]			√	√	√	√

[1] Pre-procedure Screening assessments to take place within 21 days prior to undergoing the procedure.
[2] Up to two urine pregnancy tests must be obtained prior to study procedure for females with child-bearing potential (one at pre-procedure screening and one on the day of the procedure prior to the procedure if screening and procedure are not performed on the same day).
[3] Digital photographs of the subject's face will be taken and labeled according to Photography Instructions.
[4] To be completed by Investigator and Independent Photographic Reviewers (IPRs).
[5] To be completed by the study subject on a day of the procedure (prior to the procedure and immediately following the procedure) and at all follow-up visits.
[6] To be completed by the study subject daily starting from the day of procedure (after procedure, at home) until the 10 day follow-up visit.
[7] To be completed by Investigator and/or Independent Photographic Reviewer (as applicable) to capture achievement of epidermal recovery status at follow-up visits; and date when study subject felt comfortable, willing and able to go in public following study procedure (assessed at the 10 day follow-up visit).
[8] To be completed by Investigator and study subject at all study follow-up visits.

6.5 Data Collection

Subject demographic information, procedural data, adverse events, device observations, and study required assessments will be documented on the CRFs. Study subjects will complete Visual Analog Scale and Modified Global Aesthetic Improvement Scale (GAIS): Subject Form at follow-up visits.

6.6 Confidentiality of Data

The Principal Investigator will oversee the conduct of the study and all data will be kept confidential. Confidentiality will be maintained by using subject identification numbers instead of names. Informed consent forms, data collection sheets and records, linking a subject's name with their ID number will be maintained in a locked cabinet or locked office. Information to be stored on the computer will be identified by subject ID and will be password protected.

Data disclosed outside the study team will be de-identified or will only include general group demographic information. Protected Health Information and/or identifiable study data will not be shared with anyone outside the study team or Health System, with the exception of the study sponsor, and federal regulators/ institutional officials for the purposes of auditing.

7 EVALUATION TOOLS

The following evaluation tools will be used in this study:

7.1 Fitzpatrick Skin Scale (FSS)

Assessment of subject's skin color will be determined prior to study procedure by the Investigator using the FSS. The scale delineates skin color into the categories as shown in Table 2.

Table 2: Fitzpatrick Skin Scale Evaluation

Skin Type	Description
Type I	White skin that never tans and always burns easily
Type II	White skin that tans slightly and always burns easily
Type III	Light brown skin that tans gradually and can burn moderately
Type IV	Moderately brown skin that tans well and burns slightly
Type V	Dark brown skin that tans profusely and burns rarely
Type VI	Black skin with deep pigmentation that never burns

7.2 Fitzpatrick Wrinkle and Elastosis Scale (FWS)

Assessment of subject wrinkles at baseline and follow-up visits will be performed by the Investigator and assessment of subject wrinkles at baseline and follow-up visits (excluding the 10 day follow-up visit) will be performed by three board-certified dermatologists or plastic surgeons sourced and managed by Canfield Scientific, called Independent Photographic Reviewers (IPRs), using the Fitzpatrick Wrinkle and Elastosis Scale (FWS) categories as shown in Table 3 (see also Section 12.3 Data Management Responsibilities and Section 12.3 Data Capture Methods). The FWS is a clinically validated assessment tool used to assess skin wrinkle severity and elastosis on a scale from 1 through 9, where the lower score is considered better. Three Independent Photographic Reviewers will be blinded to the study subject's visit (baseline and all applicable follow-up visits) and will perform photographic assessments of each subject's wrinkle depth in the treated zones (identified only as "Zones to Evaluate" to the IPRs) using FWS and ignoring nasolabial folds and marionette lines (effects of gravity), and artifacts from the chin rest. The IPRs will assign a single FWS score per subject at each time point.

Each photograph will have a unique identification number, but they will not be arranged in any specific order.

A subject will be considered a success if at least 2 out of the 3 IPRs agree that the subject has reached at least one degree of wrinkle score reduction per FWS when comparing the score obtained at the 3 month follow-up visit to the baseline wrinkle score.

Table 3: Fitzpatrick Wrinkle and Elastosis Scale			
Class	**Description**	**Score**	**Description**
I	Fine wrinkles	**1-3**	**Mild:** Fine texture changes with subtly accentuated skin lines.
II	Fine to moderate depth wrinkles, Moderate number of lines	**4-6**	**Moderate:** Distinct papular elastosis (individual papules with yellow translucency under direct lighting) and dyschromia
III	Fine to deep wrinkles, numerous lines, with or without redundant skin folds	**7-9**	**Severe:** Multipapular and confluent elastosis (thickened, yellow and pallid) approaching or consistent with cutis rhomboidalis.

7.3 Modified Global Aesthetic Improvement Scale (GAIS)

The Global Aesthetic Improvement Scale (GAIS) is a subjective rating of improvement in treatment results compared to pre-treatment. A modification of the GAIS to include "much worse" and "very much worse" as rating options will be used in this study. The Investigator will grade the overall improvement of treatment area as indicated in Table 4a by comparing the subject's appearance at follow-up visits against a photograph taken prior to procedure. Likewise, the subject will also rate their improvement compared to pre-treatment as shown in Table 4b.

The modified GAIS results will be collected at all follow-up visits.

Table 4a: Modified Global Aesthetic Improvement Scale Evaluation (GAIS): Investigator	
Rating	**Description**
Very much improved	Optimal cosmetic result from this procedure in this subject
Much improved	Marked improvement in appearance from the initial condition, but not completely optimal for this subject
Improved	Obvious improvement in appearance from the initial condition
No change	The appearance is essentially the same as the original condition
Worse	The appearance is worse than the original condition
Much worse	The appearance is much worse than the original condition
Very much worse	The appearance is very much worse than the original condition

Table 4b: Modified Global Aesthetic Improvement Scale Evaluation (GAIS): Subject	
Rating	
Very much improved	☐
Much improved	☐
Improved	☐
No change	☐
Worse	☐
Much worse	☐
Very much worse	☐

7.4 Re-epithelization and Down Time

The study investigators and/or Independent Photographic Reviewers (as applicable) will be required to obtain and document re-epithelization and down time defined as per below:

1. Achievement of **Re-epithelization -** determine percentage epidermal recovery per treatment zone at all follow-up visits.
2. **Down Time** - date when study subject felt comfortable, willing and able to go in public following study procedure (assessed at the 10 day follow-up visit).

7.5 Visual Analog Scale (VAS)

The study subjects will be asked to complete a 10-point Visual Analog Scale (VAS) for the following assessments:

1. Level of pain and discomfort associated with study procedure – to be completed by the subjects on the day of the procedure (prior to the procedure and immediately following the procedure), daily between the date of the procedure (reported at home) and the 10 day follow-up visit, and at all follow-up visits.
2. Subject satisfaction with treatment – at all follow-up visits. Additionally, the subjects will be asked if they would recommend the treatment to friends and acquaintances (yes, perhaps, or no)

Scoring will consist of making a mark on a 10-cm line demarcated at 1-cm intervals. Each end of the line will be awarded a score of 0 or 10 according to the extreme points of reference pertaining to an individual measure.

7.6 Subject Diary

Study subjects will be asked to complete a daily diary (see Appendix C: Subject Diary) starting from the procedure date (after study procedure, at home) until the 10 day follow-up visit to complete daily 10-point VAS pain assessments and document any complications they have experienced.

7.7 Blinded Identification of 3-Month Images

Assessment of each subject's baseline and 3-month follow-up images viewed simultaneously will be performed by the Independent Photographic Reviewers who will be blinded to the study subject's visit (baseline and 3-month follow-up visit). Each IPR will view each subject's randomized baseline and 3-month follow-up images and assess which set of images represent the subject's post-treatment images. Each photograph will have a unique identification number, but the sets of images will not be arranged in any specific order.

A subject will be considered a success if at least 2 out of the 3 IPRs correctly identify the 3-month images.

8 ADVERSE EVENTS ASSESSMENT REPORTING

8.1 Adverse Events Evaluation

Safety evaluations for this study include an interview with the study subject at each follow-up visit by the Investigator or Research Coordinator to elicit information about any medical occurrence that meets the definition of Adverse Event. This information will be documented in CRF without regard for cause or relation to device and/or procedure.

In addition, study subjects will be instructed to report all of complications experienced post study procedure to the site personnel as soon as they occur/are observed.

It is the Investigator's responsibility to determine seriousness, severity, and relatedness of the Adverse Event to the device and procedure using the definitions below.

8.2 Adverse Event (AE) Definition

An **adverse event** (AE) is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

A preexisting condition (one that is present at the start of the study) will be recorded as an AE only if the frequency, intensity, or the character of the condition worsens during the study period.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an AE in the following circumstances: hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should not be reported as an outcome of an AE if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.

8.3 Serious Adverse Event (SAE) Definition

Serious Adverse Event (SAE) is an adverse event that:

- Led to a death or
- Led to a serious deterioration in the health of a subject that:
  - Resulted in a life-threatening illness or injury,
  - Resulted in a permanent impairment of a body structure or body function,
  - Required in-patient hospitalization or prolongation of existing hospitalization,
  - Resulted in medical or surgical intervention to prevent impairment to body structure or a body function, or
  - Led to fetal distress, fetal death or a congenital abnormality or birth defect.

All SAEs that occur during the study period, whether considered to be related to the investigational product or not, must be reported to the Sponsor within 24 hours of knowledge of the event. IRB reporting requirements may also apply for SAEs.

8.4 Unanticipated Adverse Device Effect (UADEs) Definition

An **unanticipated adverse device effect** (**UADEs)** is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

In addition, any **UADEs** will be reported to the Sponsor and the reviewing IRB as soon as possible, but no later than within 24 hours of knowledge of the event.

All adverse events, anticipated or unanticipated, will be monitored until they are adequately resolved or explained.

8.5 Reporting Requirements

All adverse events (AEs) observed by study subjects, investigators or other study staff from first exposure to the study product through last study follow-up visit will be recorded. If a device-related AE, SAE, or unanticipated serious device related effect is ongoing at the final study visit, the subject will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or the subject is lost to follow-up. The investigator should make every effort to ensure that follow-up includes any supplemental investigations as may be indicated to elucidate, as completely as practical, the nature and/or causality of the AE or SAE. This may include unscheduled follow up visits for AE assessment.

Study subjects will be instructed to report all AEs to the clinical study staff. AE information will be collected throughout the study, and recorded on CRFs.

8.6 Severity of Adverse Events

The **severity of adverse events** will be categorized using the following criteria:

- **Mild:** easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities. These events generally do not require treatment.
- **Moderate:** sufficiently discomforting to interfere with normal everyday activities. These vents are usually relieved by simple therapeutic measures.
- **Severe:** prevents normal, everyday activities. These events may require systemic drug therapy or other medical treatment.

8.7 Relationship to the Study Device and/or Procedure

The **relationship to the study device and/or procedure** will be determined by the investigator utilizing the following categories:

- **Not Related:** An event for which an alternative explanation is conclusively identified – e.g., concomitant drug(s), concomitant disease(s), and/or the relationship in time suggests that a causal relationship is highly unlikely.
- **Related:** The adverse event follows a reasonable temporal sequence related to treatment by the device, follows a known or suspected response pattern and a plausible alternative etiology cannot be identified.

- **Undetermined:** The relation of the adverse event has some temporal relationship to the device and/or device procedure, is not clearly due to another condition and the involvement of the study device is unknown.

9 RISK AND BENEFITS

9.1 Benefits

A possible benefit of using J-Plasma is the potential for improvement in wrinkle severity. Additional potential benefits of improving the appearance of wrinkles could include enhanced well-being, with improved satisfaction with the appearance of less facial wrinkles or the perception of a having a more youthful appearance.

9.2 Risks

Potential risks with J-Plasma are similar to those that are encountered for many routine facial soft tissue reductions. These include but are not limited to:

- pain,
- tenderness,
- itching,
- bleeding,
- bruising/hematoma/seroma,
- allergic reaction,
- hypersensitivity to the treatment (resulting in erythema, swelling, induration and/or urticaria),
- post-inflammatory hyperpigmentation,
- telangiectasias,
- skin overheating/burn,
- hypertrophic scarring
- calcification,
- discoloration/permanent hypopigmentation,
- loss of correction,
- vessel laceration or occlusion,
- abscess at treatment site which may result in induration and/or scar formation, and
- prolonged wound healing.

Subjects using drugs that reduce coagulation (aspirin or NSAIDs) may experience increased bruising or bleeding at the treatment site.

Additionally, other wrinkle reduction products have shown rare occurrences of the following symptoms:

- systemic events such as flu-like symptoms (such as fever, headache, myalgia, neuralgia, nausea, malaise or dizziness),
- pruritis,
- shedding,
- flaking,

- scaling,
- peeling,
- rash,
- transient visual disturbances (blurred vision),
- tingling,
- numbness,
- transient polyarthralgia,
- infection,
- anaphylactic response (hypotension, difficulty breathing, tightness in chest, and/or shortness of breath).

Side effects of Tumescent anesthesia containing lidocaine or epinephrine include:

- Nausea
- Vomiting
- Mild sleepiness

9.3 Mitigation of Risks

These risks are mitigated by utilizing qualified clinical Investigators who have training and are experienced in wrinkle reduction procedures and following study treatment procedures. In addition, risks are mitigated by including only those subjects that meet the study eligibility criteria. This study also includes evaluation of study subject satisfaction with this procedure. Given the anticipated acceptable risk, the risk-benefit assessment of the use of J-Plasma for use in dermal skin resurfacing appears to offer a substantial clinical benefit at a reasonable risk.

10 STUDY MANAGEMENT/COMPLIANCE/ QUALITY ASSURANCE

10.1 Protocol Deviation Reporting

A protocol deviation is an event in which the investigator or site personnel did not conduct the study in accordance with the protocol or the Clinical Trial Agreement. Prior approval by the Sponsor is expected in situations where the Investigator anticipates, contemplates, or makes a conscious decision to deviate. Prior approval is not required when a deviation is necessary to protect the life or physical well-being of a subject in an emergency. Prior approval is not expected in situations where unforeseen circumstances are beyond the Investigator's control (e.g. inadvertent errors, product failure, or inability to perform required procedures due to subject's illness).

All protocol deviations are to be reported to the Sponsor, along with the justification for the deviation, on the Protocol Deviation CRF. Protocol deviations should be reported as soon as possible upon center notification of the deviation.

10.2 Discontinuation of Study Subjects

A subject may discontinue from the study at any time without any penalty or loss of benefits to which the subject is otherwise entitled. An Investigator may also discontinue a subject from the study without the subject's consent, if the Investigator feels it is in the best medical interest of the subject. The date and the reason for study withdrawal will be indicated on the Study Exit CRF. Every effort should be made to contact subjects lost to follow-up, and all such efforts should be documented in the subject's file.

10.3 Supply of Study Materials

Each clinical site will be provided with the investigational devices. A Device Accountability Log will be used to track the receipt, use and return of study devices at each study site. All investigational devices will be returned to study Sponsor after enrollment of all subjects. Study Sponsor will provide appropriate packaging and shipping instructions to the study sites.

10.4 Device Malfunction/Observations

All malfunctions of, or defects of the delivery system will be recorded on the Device Malfunction/Observation Case Report Form and reported to the Sponsor by the investigational sites. This will include situations where the delivery system did not perform as intended; user errors; study device/component being physically defective, including out of the box failure.

10.5 Monitoring

It is the responsibility of the study Sponsor to ensure that proper monitoring of this clinical investigation is conducted. Appropriately trained personnel appointed by the Sponsor will conduct monitoring activities, as needed, and ensure that the investigation is conducted in accordance with the study protocol, the Clinical Trial Agreement, applicable laws and regulations, including ICH GCP, and overseeing IRBs.

Prior to study initiation at each investigational site, approval to enroll subjects will be given by the Sponsor and/or designee.

The Sponsor will determine frequency and timing of interim or periodic monitoring visits for each site based on enrollment rate, volume, study compliance, and findings from previous visits. Each enrolling site will be visited at least annually. During a monitoring visit, the Monitor will evaluate the site's compliance with regulatory and protocol requirements, verify data recorded on CRFs to available source documents, etc.

In addition, the Monitor will check whether all AEs and SAEs have been reported appropriately within the time periods required.

Data Clarification Forms (DCFs) will be created for identified errors on CRFs that have been submitted to the Sponsor to ensure errors/omissions are corrected. New and previous findings and recommended corrective and preventative actions, if they exist, will be communicated with the study staff during the visit, and will also be addressed in a final letter that will be sent to the Investigator after the visit.

10.6 End of Study

The end of study will be defined as completion of all study visits by all enrolled subjects. If a device-related AE, SAE, or unanticipated serious device-related effect is ongoing at the final study visit, the subject will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or the subject is lost to follow-up.

Study closure visits may be conducted at all clinical sites in order to review record retention requirements, device disposition requirements, etc., with site personnel. The Sponsor may choose to conduct the closure visit via telephone contact if appropriate.

10.6.1 Premature Termination or Suspension of the Study or a Study Site

The study or parts of the study may be prematurely terminated or suspended by the Sponsor. This discontinuation may be based on a significant number of AEs of a similar nature that warrant such action. Furthermore, the study may be prematurely ended if the regulatory authority or the IRB make a recommendation to terminate or suspend approval for the study, the study site, or the Investigator.

If the study is prematurely terminated or suspended for any reason, the investigator must inform the subjects and assure appropriate follow-up treatment. Within the timeframes noted in applicable regulations, the Sponsor will promptly inform the investigators, study sites, the IRB, and regulatory authorities of the termination or suspension of the study, as appropriate

10.7 Audits / Inspections

The Sponsor, their designee, and the reviewing IRB may monitor or audit the study centers. Likewise, regulatory authorities may inspect Sponsor or CRO files or any study center to evaluate the conduct of the study. The Investigator must allow access to the subject files and inspection of their clinical research protocol procedures when requested.

11 STATISTICAL METHODOLOGY

This section describes the statistical analyses foreseen at the time of study planning.

Any deviations from planned analyses, the reasons for such deviation, and all alternative or additional statistical analyses that may be performed before database close will be summarized in the Clinical Study Report.

11.1 Determination of Sample Size

The objective of this study is to demonstrate that study participants positively respond to the J-Plasma® therapy, thus the primary endpoint will be assessed via the percentage of study participants that demonstrated an improvement in the FWS from baseline to the 3-month visit. An improvement is clinically important when there is ≥ 1-score change. The planned sample size to provide sufficient power for a statistical comparison of the proportion of treatment responders (P) versus a reasonable cutoff (P_0) was based on a power calculation utilizing the (one proportion) binomial exact test based on the following assumptions.

- H_0: $P \leq P_0$ versus H_a: $P > P_0$
- Type I error rate: $\alpha = 0.05$ (one-sided)
- Population proportion under the null hypothesis: $P_0 = 0.75$
- Population proportion under the alternative hypothesis: $P = 0.90$
- Total N: 50 study participants

Based on the above assumptions, the study power is estimated to be approximately 88%. To account for possible missing data (up to 10% attrition), a total of 55 subjects will be enrolled. Other tests (i.e., a test of the mean improvement of FWS) would be expected to provide more power.

One study investigating the effects of radiofrequency energy on the improvement of appearance of wrinkles and rhytides (De Novo, Newa™) utilized a FWS cutoff as 75%, supporting this value in the present sample size computation.[13]

11.2 Analysis Sets

The full analysis set (FAS) will be used for analysis of this study.

11.2.1 Full Analysis Set (FAS)

All subjects enrolled in the study who have a FWS value at baseline will be included in the FAS. Subjects with missing FWS data at the 3-month visit will be imputed as no change and included in the FAS population.

11.2.2 Per Protocol Set (PPS)

The PPS is the subset of subjects in the FAS without major protocol deviations. Major protocol deviations will be decided and finalized at a data review meeting (DRM) that will be conducted prior to database lock. The efficacy analyses will be repeated on the PP population if there is at least a 10% difference in the number of subjects in the PPS and intent-to-treat (ITT) populations.

11.3 Endpoints for Analysis

11.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the comparison of the proportion of subjects (i.e. percentage of treatment responders) with a ≥ 1-score improvement on the FWS at the 3-month visit, as compared to baseline as determined by at least 2 out of 3 blinded Independent Photographic Reviewers. The study design assumes a 75% success rate of subjects with treated wrinkles with a ≥ 1-score change on the FWS; therefore, greater than 75% of subjects must be rated with a ≥ 1-score improvement 3 months after treatment and must be statistically significantly greater than 75%.

11.3.2 Secondary Efficacy Endpoint

Subjects with a ≥ 1-score improvement on the FWS and at least a self-reported "improved" rating on the modified GAIS at the 3-month visit will be considered to have an aesthetic pleasing outcome. The modified GAIS is a measure of aesthetic improvement relative to the baseline, pre-treatment condition.

11.4 Statistical Analysis for Safety Variables

11.4.1 Primary Safety Variable

The primary safety variable is the evaluation of adverse events up to the 3-month visit after treatment. Adverse events reported at each scheduled study visit, as well as adverse events self-reported in the Subject Diary (see Appendix C: Subject Diary), will be summarized. A descriptive analysis including type, onset after treatment, duration, severity, and relationship to study device and/or procedure will be provided. With the same descriptive methodology, the duration of adverse events will be summarized with a delineation from 0-7 days, 8-14 days, 15-28 days, and more than 28 days.

11.4.2 Secondary Safety Variables

The secondary safety variable is the evaluation of the pain and discomfort after treatment as reported by the subject on a 10-point visual analog scale (VAS). Results of the VAS on a scale of 0 (no pain) to 10 (most severe pain) and the change from baseline will be summarized descriptively utilizing mean, standard deviation, minimum, maximum, median, and the 95% confidence interval of the mean and mean change from baseline.

11.5 Additional Endpoints

Other endpoints to be evaluated include:

1. FWS ≥ 1-score improvement and ≥ 75% agreement with at least an "improved" rating by the subject on the modified GAIS. The modified GAIS is a measure of aesthetic improvement relative to the baseline, pre-treatment condition.
2. Magnitude of improvement measured by the mean change in FWS from baseline to 3-month visit.
3. Subject satisfaction with procedure recorded at the 3-month visit.

4. Achievement of re-epithelialization by facial zone (and across facial zones) at the 10-day, 1-month and 3-month follow-up visits as reported by the study investigator and/or Independent Photographic Reviewers (as applicable).
5. Mean duration until subject feels comfortable going in public after treatment as reported the study subject.
6. Daily 10-point Visual Analog Scale (VAS) pain assessments following treatment through the 10 day follow-up visit by diary day with a change from the VAS pain score at baseline.
7. The proportion of subjects (i.e. percentage of treatment responders) with correct identification of 3-month images, in comparison to baseline, as determined by at least 2 out of 3 blinded Independent Photographic Reviewers.

11.6 Statistical Analysis for Efficacy and Additional Endpoints

Endpoint	Variable	Statistical analyses
Primary efficacy endpoint	Percentage of subjects with a ≥ 1-score improvement on the FWS from baseline to 3-month visit	The percentage of subjects with a ≥ 1-score improvement will be summarized as counts and percentages. This percentage will be compared to the cutoff of 75% using a binomial exact test (one-sided). Descriptive upper 95% confidence limit will be provided for the difference between treatment and cutoff rate and the associated p-value will also be provided.
Secondary efficacy endpoint	Investigator – Modified GAIS	An "improvement" on the modified GAIS by the treating investigator at the 3-month visit will be classified as "improved," "much improved," or "very much improved." All other ratings on the modified GAIS will be classified as "no improvement." Cross-tabulation of improvement status of modified GAIS versus 1-score FWS response will then be summarized as counts and percentages.
Primary safety variable	Adverse event rate	Adverse event rates (total and categorized by duration) will be summarized as counts and percentages. Stratification on type, onset after treatment, duration, severity, and relationship to study device and/or procedure will also be provided.
Secondary safety variable	Study Subject - Pain/Discomfort VAS after treatment	Evaluation of pain and discomfort after treatment (and the change from baseline) as reported by the subject on a 10-point visual analog scale (VAS). Results of the VAS on a scale of 0 to 10 will be summarized descriptively utilizing mean, standard deviation, minimum, maximum, median, and the 95% confidence interval of the mean and mean change from baseline.
Additional endpoint #1	Study Subject – Modified GAIS	An "improvement" on the modified GAIS by the subject at the 3-month visit will be classified as "improved," "much improved," or "very much improved." All other ratings on the modified GAIS will be classified as "no improvement." Cross-tabulation of improvement status of modified GAIS versus 1-score FWS response will then be summarized as counts and percentages.
Additional endpoint #2	Mean change in FWS from baseline to 3-	Descriptive summary statistics (number of observations, mean, standard deviation, minimum, maximum, median,

	month visit	95% confidence interval of the mean) will be used for summarizing the change in FWS from baseline to the 3-month visit. The FWS from baseline to the 3-month visit will also be stratified on both the treating-investigator and subject modified GAIS.
Additional endpoint #3	Study subject satisfaction at 3-month visit	Evaluation of the subject satisfaction as reported by the subject on a visual analog scale (VAS). Results of VAS on a scale of 0 to 10 will be summarized descriptively utilizing mean, standard deviation, minimum, maximum, median, and the 95% confidence interval of the mean. Cross tabulation of subject satisfaction/improvement versus 1-score FWS response will be summarized as counts and percentages.
Additional endpoint #4	Achievement of re-epithelialization by facial zone and across facial zones after treatment	Descriptive summary statistics (number of observations, mean, standard deviation, minimum, maximum, median, 95% confidence interval of the mean) will be used for summarizing the achievement of re-epithelialization by facial zone and across facial zones at all follow-up visits through the 3-month visit.
Additional endpoint #5	Mean duration for study subject to feel comfortable in public after treatment	Descriptive summary statistics (number of observations, mean, standard deviation, minimum, maximum, median, 95% confidence interval of the mean) will be used for summarizing the mean duration for study subject to feel comfortable after treatment.
Additional endpoint #6	Study Subject - Pain/Discomfort VAS after treatment through the 10 day follow-up visit	Descriptive summary statistics by diary day (number of observations, mean, standard deviation, minimum, maximum, median, 95% confidence interval of the mean) and the change from the VAS pain score at baseline will be provided.
Additional endpoint #7	Percentage of subjects with correct identification of 3 month image	The percentage of subjects with correct identification of 3-month images will be summarized as count, percentage, and 95% exact binomial confidence interval.

11.7 Subgroup Analysis

Subgroup analyses will include stratifying the primary endpoint (percent treatment responders on FWS), on age, gender, race/ethnicity, and Fitzpatrick Skin Scale (FSS). Additionally, the degree of improvement on FWS (e.g. 2, 3 or 4-score improvement) will be reported.

11.8 Other Statistical/Analytical Issues

11.8.1 Discontinuations and Missing Data

Subjects with missing 3-month FWS data will be imputed as having no change from baseline. No other imputations for missing data will be employed. Furthermore, no estimation of missing data for self-reported pain within the 10 day Subject Diary will be imputed.

12 DATA HANDLING AND RECORDKEEPING

12.1 Investigator Records

The Investigator is responsible for the preparation, review, signature, and retention of the records listed below:

- signed Clinical Trial Agreement and Curriculum Vitae
- all correspondence pertaining to the investigation with other investigators, the reviewing IRB, the study Sponsor, the Monitor and FDA,
- investigational device receipt, use and disposition records,
- subject case history records relating to use of the device, including Case Report Forms, medical records, progress notes, nurses notes, etc.,
- all signed informed consent forms,
- all shipping and disposition records for investigational devices and relevant observations relating to the device, and
- the protocol and documentation of date and reason for any deviation from investigational plan.

Records are subject to FDA inspection and must be retained for a period of at least two years after the latter of two dates:

1. date on which the investigation is terminated or completed, or
2. date that the records are no longer required for purposes of supporting an application to the FDA to market the device.

12.2 Investigator Reports

The Investigator is responsible for the preparation, review, signature, and submission of the reports listed in Table 5. These are also subject to the FDA inspection and the retention requirements described above for the Investigator's Records.

Table 5: Required Investigator Reports

Report	Submit to	Description
Unanticipated Adverse Device Effect (UADE)	Sponsor and IRB	The Investigator must submit to the Sponsor and reviewing IRB a report of any UADE as soon as possible but not less than 10 working days after the Investigator first learns of the effect.
Withdrawal of IRB Approval	Sponsor	The Investigator must report a withdrawal of the reviewing IRB approval within 5 working days.
Progress Report	Sponsor, Monitor and IRB	The Investigator must submit this report at regular intervals, but not less than once per year to the IRB, Sponsor and Monitor.
Deviation from Protocol in Emergency	Sponsor and IRB	Deviation from the study protocol that is made to protect the life or physical well-being of a subject in an emergency situation must be reported within 5 working days after the emergency occurred.

Deviation from Protocol that affect the scientific soundness of the study plan or the rights, safety or welfare of human subjects	Sponsor	Prior approval by the Sponsor is required when a deviation of this nature is anticipated.
Failure to obtain informed consent	Sponsor and IRB	If a study device was used without obtaining informed consent, the Investigator must notify the Sponsor and IRB within 5 working days of the use of the device.
Final Report	Sponsor and IRB	The Investigator must submit this report to the Sponsor and IRB within 3 months after the termination or completion of the study, or after the Investigator's participation in the study is complete.

12.3 Data Management Responsibilities

Data collection is the responsibility of the study staff at the site under the supervision of the site Principal Investigator. During the study, the Investigator must maintain complete and accurate documentation for the study.

Electronic Data Capture (EDC) Data management and oversight is the responsibility of North American Science Associates, Inc. (NAMSA). Responsibilities include, but are not limited to, the following:

- Clinical strategy and oversight
- Clinical study operations
- File management and study documentation
- Site initiation visits and study close-out visits
- Clinical quality assurance
- Statistical support and programming
- Data management, including database development and programming and electronic data capture (EDC) programming, training, and management

Additionally, management and oversight of photographic imaging is the responsibility of Canfield Scientific. Responsibilities include, but are not limited to, the following:

- Providing photographic equipment and supplies as well as installation and training at each investigational site
- Project management of photographic imaging throughout the investigation
- Preparation of the User Manual for use during the study to ensure consistent serial photography is achieved
- Monitoring and quality review of incoming images
- Digital image management and storage
- Management of all independent photographic panel review activities, including sourcing and contracting independent reviewers, facilitating reviews, and transferring the data per an approved Data Transfer Agreement

12.4 Data Capture Methods

Electronic Data Capture (EDC) will be utilized in the investigation. NAMSA is responsible for creating the EDC system as well as training all sites and Sponsor on the EDC system, hosting the database/servers, and reviewing and correcting the data.

Photographic images will be captured utilizing the Canfield Scientific Visia-CR 2.3 system as specified in the Canfield User Manual for the study.

13 PUBLICATION POLICY

The publication policy will be in accordance with the Investigator Agreement with each Principal Investigator or similar agreement.

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Appendices