Advarra IRB Approval Date : August 27th 2018

NCT03690375

ID: Purpura001
Robyn Siperstein, MD

Documents Enlcosed:

1. Statistical Analysis Plan
2. Protocol

STATISTICAL ANALYSIS PLAN

Primary Endpoint

$H_0: \mu_C = 0$; $H_1: \mu_C > 0$

- The null hypothesis is the absolute mean difference in the change from baseline to 30 days after the last treatment on the treatment arm as compared to the non-treatment arm is zero.
- The alternative hypothesis is the absolute mean change from baseline to 30 days after the last treatment on the treatment arm as compared to the non-treatment arm is greater than zero.

1. Let μ_C represent the absolute mean difference between the treated arm as compared to the non-treated arm in the difference in the number of ecchymoses from baseline to 30 days after the last treatment.

2. Let μ_C represent the absolute mean difference between the treated arm as compared to the non-treated arm in the difference in the size of ecchymoses from baseline to 30 days after the last treatment.

A Paired t-test will be used to analyze the primary endpoint. The results of the statistical analysis will be presented as an odds ratio with 95% Confidence intervals. A Shapiro-Wilk Test will be used to assess the normality of data.

PROTOCOL

A Prospective, Randomized, Split-Arm Clinical Study Investigating the Efficacy and Safety of Sciton's Broad Band for the Treatment and Prevention of Senile Purpura

Pilot Study

Robyn Siperstein M.D.

A Prospective, Randomized, Split-Arm Clinical Study Investigating the Efficacy and Safety of Sciton's Broad Band for the Treatment and Prevention of Senile Purpura

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the ICH E6 and the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator: Robyn Siperstein

Signed: _____ Date: _____ Signature

1 PROTOCOL SUMMARY

Title: A Prospective, Randomized, Split-Arm Clinical Study Investigating the Efficacy and Safety of Sciton's Broad Band for the Treatment and Prevention of Senile Purpura

Précis: There will be ten subjects, 5 older subjects over 65 years of age with at least one ecchymotic lesion on each arm measuring at least one cm, and 5 subjects under 35 years of age. All subjects will be randomized to undergo 4 Sciton Broad Band Light (BBL) treatments on either their left or right arm one week apart. Subjects will fill out questionnaires, have pictures of their lower arms taken, and will be graded and measured by evaluators regarding the number and size of their ecchymoses as well as side effects such as blistering, pain, erythema, and swelling. One day after their 4th treatment, subjects will have biopsies done to be analyzed for changes in histology and gene expression. The subjects will follow up at 30 days after their last treatments for final pictures of their lower arms and evaluations.

Objectives:

Primary Objectives: To assess the efficacy of BBL in improving the appearance of senile purpura

Important Secondary Objectives:

1. To assess the safety of a new BBL protocol for treating and preventing senile purpura
2. To assess the efficacy of BBL in reducing skin tears
3. To assess the efficacy of BBL to improve the histology of the skin
4. To assess the efficacy of BBL to increase epidermal thickness
5. To assess the efficacy of BBL to change gene expression

Endpoint

Primary Endpoints:

1. Mean absolute difference in the BBL treated arms as compared to the non-treated arms of those with senile purpura in the total square area of purpuric lesions from the first treatment to 30 days after the last treatment
2. Mean absolute difference in the BBL treated arms as compared to the non-treated arms of those with senile purpura in the number of purpuric lesions from the first treatment to 30 days after the last treatment

Important Secondary Endpoints:

1. Measurement of pain, swelling, blistering, erythema, and all side-effects immediately after each procedure, as well as 24 hours, 48 hours, and 7 days after the procedure.

2. Mean absolute difference in the number of skin tears at baseline and 30 days after the last treatment
3. The changes in collagen and elastin between untreated and treated skin
4. Mean absolute difference in the change in epidermal thickness between treated and untreated skin
5. Changes in gene expression between treated and untreated skin

Population:	Sample size 10 Male and female adults over the age of 21 living in Palm Beach County Florida.
Number of Sites	1
Study Agent:	Sciton's BBL
Study Duration:	51 days

SCHEMATIC OF STUDY DESIGN

Day -30 to 0 Screening

- Total n=10
- Obtain informed consent
- Screen potential subjects by inclusion and exclusion criteria (Eligibility Questionnaire)

Day 0: Randomization

- Subjects randomized to have BBL on either their left or right

Day 0: Baseline assessments/ Study Intervention

- Baseline Assessments:
  Pre-procedure pictures of patient's lower arms taken with a Digital Camera

  Baseline assessment and measurement by evaluator

  Baseline Medical History and Medication questionnaires completed by all subjects
- Study Intervention #1:
  Sciton's BBL done according to purpura protocol on one arm according to randomized assignment
- Post-Procedure Assessments:
  Post-procedure questionnaires filled out by all subjects

Day 1: Follow-up assessments

- At Home Follow-up Assessments Questionnaire Regarding Side-Effects

Day 2: Follow-up assessments

- At Home Follow-up Assessments Questionnaire Regarding Side-Effects

Day 7 +/- 2 Days: Follow-up assessments / Study Intervention

- Follow-up assessments:
  Evaluator assessment and measurement

  Pictures taken of subject's lower arms

  Subject follow up questionnaires filled out by all subjects
- Study Intervention #2:
  Sciton's BBL done a second time on the assigned arm according to protocol settings
- Post-Procedure Assessments:

Post-procedure questionnaires filled out by all subjects immediately after treatment

Day 14 +/- 2 Days: Follow-up assessments / Study Intervention

- Follow-up assessments:
  Evaluator assessment and measurement
  Pictures taken of subject's lower arms

  Subject follow up questionnaires filled out by all subjects

- Study Intervention #3:
  Sciton's BBL done a third time on the assigned arm according to protocol settings
- Post-Procedure Assessments:
  Post-procedure questionnaires filled out by all subjects immediately after treatment

Day 21 +/- 2 Days: Follow-up assessments / Study Intervention

- Follow-up assessments:
  Evaluator assessment and measurement

  Pictures taken of subject's lower arms

  Subject follow up questionnaires filled out by all subjects

- Study Intervention #4:
  Sciton's BBL done a fourth time on the assigned arm according to protocol settings
- Post-Procedure Assessments:
  Post-procedure questionnaires filled out by all subjects immediately after treatment

Day 22 +/- 2 Days: Follow-up assessment via skin biopsy

- A 4mm punch biopsy will be done on both the treated and untreated arm approximately 4cm below the crease in the antecubital fossa

Day 51 +/- 2 Days: Follow-up assessment

- Follow-up assessments:
  Evaluator assessment and measurement

  Pictures taken of subject's lower arms

  Subjects follow up questionnaires filled out by all subjects

2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

Senile Purpura is a benign common condition characterized by recurrent formation of ecchymosis on the extensor surfaces of forearms and hands following minor trauma. Other names of this condition are Bateman purpura, named after British dermatologist Thomas Bateman, who first described it in 1818, and actinic purpura, because of its association with sun damage (1).

More recently in 2007, Kaya and Saurat coined the term dermatoporosis to describe the chronic cutaneous fragility of aging skin. Dermatoporosis features include thinning atrophic skin, purpura, skin lacerations and delayed healing (2).

This condition affects over 10% of those aged over 65 years old and is equally common in males and females. Risk factors are known to include the use of oral or topical corticosteroids and anti-coagulants (3).

With age and sun damage, the dermis becomes thin. As a result, this condition results from superficial vessels tearing even with negligible trauma. The subsequent extravasation of blood into the surrounding dermis results in the development of ecchymosis. Histologically, the epidermis is thinned and the dermis demonstrates significantly reduced amounts of collagen replaced by abnormal elastic fibers, as well as extravasated red blood cells (4).

Intense pulsed light (IPL) is non-coherent, non-collimated, polychromatic light energy. IPL emits different wavelengths that target specific chromophores. This makes IPL a versatile therapy with many applications, from the treatment of pigmented or vascular lesions to hair removal and skin rejuvenation. Its large spot size ensures a high skin coverage rate and ease of use over large areas. The treatment has very little downtime given its non-ablative nature which makes it an attractive option. In many cases, IPL is similar to laser therapy in effectiveness, convenience, and safety and together with its versatility will lead to an expanded range of applications and possibilities in the future.

Relevant Clinical Research

Published studies on treatments for senile or actinic purpura or dermatoporosis are very limited. In one small double blinded study (N=14) published in 1995 in The Archives of Dermatology, they showed twice daily treatment with retinoic acid cream resulted in significant reduction in Bateman's actinic purpura after two weeks, however there were no significant differences after that time (6).

Multiple studies have shown the efficacy of topical Retinol and Tretinoin in increasing epidermal thickness and one study in particular in the Journal of Cosmetic Dermatology in 2016 showed not only an increased thickness in the epidermis but also up-regulated genes for Collagen Type 1 (COL1A1) and Collagen Type 3 (COL3A1) with corresponding increases in procollagen 1 and procollagen 3 protein expression (7).

A very small study (N=6) on the effectiveness of human epidermal growth factor for the treatment of actinic purpura when applied twice daily for six weeks showed an increase epidermal thickness on ultrasound and the mean number of lesions decreased from 15 to 2.3 (8).

More recently in 2017, Ceilley published his experience with DerMend in the Journal of Cllinical and Aesthetic Dermatology, reviewing why he thought a topical preparation with Retinol, Alpha hydroxyl acids, Arnica oil, Ceramindes, Niacinamide, and Phytonadione would be an optimal treatment for this condition (3).

The current literature supports the ability of IPL to induce collagen neogenesis. Studies on mice showed that IPL treatments significantly increased the number of collagen and elastic fibers within the dermis and improved the parallel distribution of collagen fibers in relation to the epidermis. These results were only evident after three IPL treatments spaced 2 weeks apart and not after just one or two treatments (5). In a study with rats, IPL increased dermal collagen fibers and collagen fiber diameter after 3 weeks (9) and in another study on rats, IPL increased dermal thickness, density of collagen, the hydroxyproline content, and the expression of III procollagen mRNA (18). In one study in humans, 5 patients showed histological evidence of new collagen formation 6 months after four IPL treatments (19). The current literature not only supports the ability of IPL to induce collagen neogenesis but also microneedling and microneedling with radiofrequency. One study showed microneedling resulted in greater skin and dermal thickness than IPL and increased expression of Type 1 collagen and total collagen content (20).

In Patrick Bitter's pilot study published in 2015 in the Journal of Cosmetic Dermatology, they used 3'-end sequencing for expression quantification ("3-seq") to discover the gene expression associated with human skin aging and the impact of broadband light (BBL) treatment. In the study skin aging was associated with a significantly altered expression of 2,265 coding and noncoding RNAs, of which 1,293 became "rejuvenated" after BBL treatment (more similar to expression levels in youthful skin). Rejuvenated genes (RGs) included several known key regulators of organismal longevity (16). Hence, according to this study, BBL treatment appears to be able to restore gene expression pattern of photo aged and intrinsically aged human skin to resemble young skin and therefore may be an ideal treatment option for senile or actinic purpura.

In addition, though most cosmetic surgeons and injectors have seen firsthand the improvement of post procedural bruising with both pulse dye lasers or intense pulse light lasers, there are limited published studies on this topic. One study published in the Archives of Plastic Surgery in 2009 showed pulsed-dye laser was effective for treating ecchymoses after facial cosmetic procedures and resulted in a 63% mean improvement in ecchymosis scores within 48 to 72 hours (14), however there are no published studies to date using IPL.

2.2 RATIONALE

The current treatments of senile or actinic purpura include oral arnica, and topical arnica, vitamin K, retin-A, retinol, growth factors, alpha hydroxyl acids, ceramides, and niacinamide. However, all of these have very limited results, if any, and there have been no large-scale studies proving their long-term efficacy for this condition.

If broadband light (BBL) is used to reduce photo-damage, decrease post-procedural purpura, is associated with a significantly altered expression of RNAs similar to that in youthful skin, and has been reported to increase collagen production and epidermal thickening, then it follows that this treatment may be an ideal option for reduction of senile purpura.

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 KNOWN POTENTIAL RISKS

Common potential risks of BBL include swelling, pain, scabbing, blistering, reduction of hair and lentigenes, erythema, pruritus, lightening and darkening of the skin, and reactivation of herpes infection. Rare but potential risks of BBL include severe burn, skin ulceration, scarring and infection.

Common potential risks of a skin biopsy include bleeding and scarring while rare but potential risks include infection and allergy to the lidocaine, bandages, or sutures used in the procedure.

2.3.2 KNOWN POTENTIAL BENEFITS

Improvement of the subject's ecchymoses leading to an aesthetic improvement. This aesthetic improvement may positively impact the subjects' psychological well-being. In addition, the treatment may lead to less skin tears by increasing the epidermal thickness which would prevent bleeding, infection risk, and scarring.

3 STUDY DESIGN, OBJECTIVES, AND ENDPOINTS

3.1 DESCRIPTION OF THE STUDY DESIGN

- A Prospective, Randomized, Split-Arm Clinical Study
- Single Center
- Study agent: Sciton's BBL
- Study Interventions: BBL Treatment on Day 0, Day 7, and Day 21
- Evaluations on Day 0, Day 7, Day 14, Day 21, Day 22, Day 51.

This will be a prospective, split-arm clinical study in which 5 subjects will be randomized to which arm will be treated with Sciton's BBL.

All subjects will have their arms shaved prior to the procedure and cleaned thoroughly with alcohol. After the procedure a zinc-based sunscreen will be applied to both arms.

Before each of the four treatments and 30 days after the last treatment, the subjects' number and square area of ecchymoses will be measured by an evaluator. Side effects will be measured on Day 0, 1, 2, 7, 14, 21, 22 and 51. Digital photography of subject's arms will be done on day 0, 7, 14, 21, and 51.

3.2 STUDY OBJECTIVES & ENDPOINTS

3.2.1 STUDY OBJECTIVE

➢Primary Objectives: To assess the efficacy of BBL in improving the appearance of senile purpura

Important Secondary Objectives:

- ➢ To assess the safety of a new BBL protocols for treating and preventing senile purpura
- ➢ To assess the long-term efficacy 30 days after all treatments have stopped
- ➢ To assess the efficacy of BBL in affecting histological changes such as epidermal thickness
- ➢ To assess the changes in mRNA after treatment

3.2.2 PRIMARY ENDPOINT

➢Primary Endpoint: Mean absolute difference between the treated and non-treated arms in the change of total square area and number of ecchymoses from baseline to 30 days after the last treatment.

3.2.3 SECONDARY ENDPOINTS

1. Measurement of pain, swelling, blistering, erythema, and all side-effects immediately after each procedure, as well as 24 hours, 48 hours, and 7 days after the procedure.
2. Mean absolute difference in the number of skin tears at baseline and 30 days after the last treatment
3. The changes in collagen and elastin between untreated and treated skin
4. Mean absolute difference in the change in epidermal thickness between treated and untreated skin
5. Changes in gene expression between treated and untreated skin

3.2.4 EXPLORATORY ENDPOINTS

Through subject questionnaires, other variables that may affect study endpoints will be explored such as smoking, dominant hand, sex, medications, and time spent in the sun.

4 STUDY ENROLLMENT AND WITHDRAWAL

4.1 PARTICIPANT INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Provision of signed and dated informed consent form
- Stated willingness to comply with all study procedures and availability for the duration of the study
- Male or female, aged >22
- In good general health as evidenced by medical history
- Ecchymosis greater than 1cm on each arm

4.2 PARTICIPANT EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

- Subjects with a history of any arm swelling
- Subjects with allergies to light
- Subjects with auto-immune skin conditions such as lupus, or vitiligo
- Subjects using topical retinol within the last 3 months
- Subjects with any scheduled laser, light, or surgical procedures on the arm during the study
- Subjects unwilling or unable to keep their arms still during digital pictures
- Subjects who are pregnant or nursing
- Subjects with a history of herpes simplex or zoster on their arms
- Subjects with current skin infections, tumors, or dermatitis on the arm
- Subjects with allergies to lidocaine
- Subjects with a history of keloid formation
- Subjects with a history of a bleeding disorder
- Subjects with allergies to adhesives

4.3 STRATEGIES FOR RECRUITMENT AND RETENTION

- Participants will be compensated by receiving $5 cash for each visit

- Subjects will receive an email, text or phone call reminder for all their scheduled visits according to their preference

- The source of the subjects will be those who visited Siperstein Dermatology Group and allowed their information to be used in order to be contacted for promotions and trials.

4.4 PARTICIPANT WITHDRAWAL ORTERMINATION

4.4.1 REASONS FOR WITHDRAWAL OR TERMINATION

Participants are free to withdraw from participation in the study at any time.

An investigator may terminate participation in the study if:

- The participant's health declines
- The participant needs any surgery or other serious medical interventions
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
- The participant fails to show up for follow-up and final visits

4.4.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

The primary investigator will attempt to visit all participants that have withdrawn or terminated from the trial if they are unable to make their follow-up visits to ensure as much data as possible has been collected and that all safety parameters have been met.

4.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the primary investigator will promptly inform the IRB as well as provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements

Study may resume once concerns about safety, protocol compliance, or data quality is addressed.

5 STUDY AGENT

5.1 STUDY EQUIPMENT

5.1.1 DEVICES FOR INTERVENTION

- Sciton's BBL, Joule Platform

5.1.2 DEVICE INDICATION

The Sciton BBL as described in the 510(k) summary for the Joule multi-platform system on which it is located, is described as a laser surgical instrument for use in general and plastic surgery and in dermatology. One of the intended uses is described as the treatment of vascular lesions. We are therefore using this device as per indication since a vascular lesion is a lesion relating to, affecting, or consisting of a vessel or vessels, especially those that carry blood and purpura is a lesion relating to the injury of blood vessels in which blood escapes into the surrounding skin. We will mainly be using the 560 and 590 cut off filters since these are the recommended filters to treat vascular lesions.

5.1.2 DURATION OF THERAPY

- The BBL treatment will take approximately 15 minutes
- The last treatment will be done on Day 21

5.1.3 OTHER EQUIPMENT NECCESARY

- Metal Goggles for participants and IPL specific wavelength goggles for investigator
- Punch Biopsy Kit

6 STUDY PROCEDURES AND SCHEDULE

6.1 STUDY PROCEDURES/EVALUATIONS

6.1.1 STUDY SPECIFIC PROCEDURES

- Medical history obtained and verbally verified
- Assigned arm meeting inclusion criteria is shaved to remove all hair
- Digital Pictures taken of bilateral hands and arms
- Counseling the subjects on the treatment that they will be receiving and post-care instructions.
- The study coordinator will check before the patient leaves that all appropriate photos and paperwork have been completed.
- BBL study treatment will be done according the protocol below outlining specific settings

BBL Only Protocol
1st Treatment Settings
1. SkinTyte Filter ST: 150 Joules, 15msec, 15 degrees for 10 continuous passes in alternating directions (5 each direction)
2. 590 Filter: 8J, 15msec, 15 degrees x 2 passes
3. 590 Filter: 10J 15msec, 15 degrees x 2 passes
4. 560 Filter: 8J, 15msec, 15 degrees x 2 passes
2nd Treatment Settings
If any answers on the post procedure side effects questionnaire from day 0,1, or 2 were SEVERE or if the patient had blisters from the previous treatment
Decrease Step 3 & 4 by 2 Joules
1. SkinTyte Filter ST: 150 Joules, 15msec, 15 degrees for 10 continuous passes in alternating directions

2. 590 Filter: 8J, 15msec, 15 degrees x 2 passes
3. 590 Filter: 8J 15msec, 15 degrees x 2 passes
4. 560 Filter: 6J, 15msec, 15 degrees x 2 passes
If any answers on the post procedure side effects questionnaire on day 0,1, or 2 were MODERATE with NO blistering
Decrease Step 3 & 4 by 1 Joule
1. SkinTyte Filter ST: 150 Joules, 15msec, 15 degrees for 10 continuous passes in alternating directions
2. 590 Filter: 8J, 15msec, 15 degrees x 2 passes
3. 590 Filter: 9J 15msec, 15 degrees x 2 passes
4. 560 Filter: 7J, 15msec, 15 degrees x 2 passes
If all answers on the post procedure side effects questionnaire on day 0,1, or 2 protocol were MINIMAL
Keep Settings the same as previous visit
1. SkinTyte Filter ST: 150 Joules, 15msec, 15 degrees for 10 continuous passes in alternating directions (5 each direction)
2. 590 Filter: 8J, 15msec, 15 degrees x 2 passes
3. 590 Filter: 10J 15msec, 15 degrees x 2 passes
4. 560 Filter: 8J, 15msec, 15 degrees x 2 passes
If all answers on the post procedure side effects questionnaire on day 0,1, or 2 protocol were NONE
Increase Step 1 by 10 additional passes and Increase Step 3 & 4 by 1 Joule
1. SkinTyte Filter ST: 150 Joules, 15msec, 15 degrees for 20 continuous passes in alternating directions (10 each direction)
2. 590 Filter: 8J, 15msec, 15 degrees x 2 passes
3. 590 Filter: 11J 15msec, 15 degrees x 2 passes
4. 560 Filter: 9J, 15msec, 15 degrees x 2 passes

3rd and 4th Treatment Settings
-If any answers on the post procedure side effect questionnaire were SEVERE or if the patient had blisters from the previous treatment
Decrease Step 3 & 4 by 2 Joules from settings at previous visit
-If any answers on the post procedure side effect questionnaire were MODERATE with NO blistering
Decrease Step 3 & 4 by 1 Joule from settings at previous visit
-If any answers on the post procedure side effect questionnaire were MINIMAL with NO blistering
Keep Settings the same as previous visit
-If all answers on the post procedure side effect questionnaire were NONE
Increase Step 1 by 10 additional passes and Increase Step 3 & 4 by 1 Joule from settings at previous visit

6.1.2 STANDARD OF CARE STUDY PROCEDURES

The patients will be cleaned with alcohol prior to treatment. After the treatment, a zinc-based sunblock will be applied and if there is any post-treatment pain a cold ice pack will be applied.

The patient will be cleaned with alcohol prior to the skin biopsy and injected with lidocaine to numb the area. Sterile equipment will be used to take a 4mm punch biopsy from the same location on each arm.

6.2 STUDY SCHEDULE

6.2.1 SCREENING

Screening Visit (Day -30 to 0)

- Review subject questionnaire to determine eligibility based on inclusion/exclusion criteria
- Schedule study visits for participants who are eligible and available for the duration of the study
- Provide participants with specific instructions needed to prepare for all their visits

6.2.2 ENROLLMENT/BASELINE

Enrollment/Baseline Visit (Visit 1, Day 0) Treatment #1

- Review in depth the study design with subjects and obtain informed consent of potential participants verified by signature
- Perform examination and verbally review subject's medications, medical history, and subject questionnaire to determine eligibility based on inclusion/exclusion criteria

- Obtain demographic information
- Shave the hair on the subjects' lower arms
- Take digital pictures of subjects' lower arms
- Have evaluator measure the size and number of bruises and skin tears
- Perform the BBL treatment on assigned arm per protocol
- Record adverse events as reported by participant or observed by investigator
- Perform protocol adherence check by study coordinator
- Expected post-procedure side effects and possible emergent situations reviewed with subjects and post-op written instructions given

6.2.3 FOLLOW UP TREATMENTS

2nd Treatment (Visit 2, Day 7 +/- 2 days)

- Record adverse events as reported by participant or observed by investigator.
- Subjects fill out adherence questionnaire and evaluator review to ensure continued eligibility
- Evaluator measures the size and number of bruises and number of skin tears
- Shave bilateral lower arms
- Take digital pictures of subjects' lower arms
- Perform the BBL treatment the second time per protocol
- Record adverse events as reported by participant or observed by investigator.
- Perform protocol adherence check by study coordinator
- Expected post-procedure side and post-op written instructions reviewed

3rd Treatment (Visit 3, Day 14 +/-2 days)

- Record adverse events as reported by participant or observed by investigator.
- Subjects fill out adherence questionnaire and evaluator review to ensure continued eligibility
- Evaluator measures the size and number of bruises and number of skin tears
- Shave bilateral lower arms
- Take digital pictures of subjects' lower arms
- Perform the BBL treatment a third time per protocol
- Record adverse events as reported by participant or observed by investigator
- Perform protocol adherence check by study coordinator
- Expected post-procedure side and post-op written instructions reviewed

4th Treatment (Visit 4, Day 21 +/-2 days)

- Record adverse events as reported by participant or observed by investigator.
- Subjects fill out adherence questionnaire and evaluator review to ensure continued eligibility
- Evaluator measures the size and number of bruises and number of skin tears
- Shave bilateral lower arms
- Take digital pictures of subjects' lower arms
- Perform a BBL treatment on the assigned arm a fourth time per protocol
- Record adverse events as reported by participant or observed by investigator.
- Perform protocol adherence check by study coordinator

- Expected post-procedure side and post-op written instructions reviewed

6.2.4 FOLLOW UP VISITS

Follow Up Visit 1 (Visit 5, Day 22 +/-2 days)

- Clean skin with alcohol
- Perform protocol adherence check by study coordinator
- Perform 4mm punch biopsy
- One dissolving suture will be placed in the dermis along with a steri-strip on the top of the skin
- Skin specimens will be bisected, and half will be placed in formalin and half will be placed in RNAlater.
- Skin specimen bottles will be coded and sent for blinded evaluation
- Expected post-procedure side and post-op written instructions reviewed

6.2.5 FINAL STUDY VISIT

Follow-up Visit 2 (Visit 6, Day 51 +/-2 days)

- Record adverse events as reported by participant or observed by investigator.
- Subjects fill out adherence questionnaire and evaluator review to ensure continued eligibility
- Evaluator measures the size and number of bruises and number of skin tears
- Shave bilateral lower arms
- Take digital pictures of subjects' lower arms
- Provide final instructions

6.2.6 EARLY TERMINATION VISIT

- Record adverse events as reported by participant or observed by investigator.
- Collect questionnaires
- Take Digital Photos of subject's lower arms
- Record participant's adherence to treatment program
- Provide final instructions

6.2.7 UNSCHEDULED VISIT

All unscheduled visits will be discouraged unless emergent. All unscheduled visits will be recorded and kept as brief as possible with no active intervention unless a vascular occlusion is suspected, or other emergent health condition is suspected.

6.2.8 SCHEDULE OF EVENTS TABLE

Procedures	Enrollment/Baseline/1st Treatment Visit 1, Day 0	2nd Treatment Visit Visit 2, Day 7	3rd Treatment Visit Visit 3, Day 14	4th Treatment Visit Visit 4, Day 21	Follow Up Visit 1 Visit 5, Day 22	Follow Up Visit 2 Visit 6, Day 51
Informed consent	X					
Demographics	X					
Medical history	X					
Subject Questionnaire	X	X	X	X		x
Study Intervention	X	X	X	X		
Evaluation for adverse effects	X	X	X	X		x
Digital photos	X	X	X	X		x
Evaluator Measurements	X	X	X	X		x
Skin Biopsy					x	

6.3 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

Changes in any anti-coagulants and prednisone use are prohibited during the study as well as any procedures or surgeries on the treatment arm.

In the event a subject makes changes to their medications or has treatments or procedures, the primary investigator will make the final decision regarding early termination from the study or disregarding certain data from final statistical analysis.

6.4 PROPHYLACTIC MEDICATIONS, TREATMENTS, AND PROCEDURES

None will be used

6.5 RESCUE MEDICATIONS, TREATMENTS, AND PROCEDURES

If patients develop an infection during the trial, they will be prescribed the appropriate anti-viral or anti-bacterial medication but will continue in the study.

7 ASSESSMENT OF SAFETY

7.1 SPECIFICATION OF SAFETY PARAMETERS

7.1.2 DEFINITION OF SERIOUSADVERSE EVENTS (SAE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32)

Serious adverse event or serious suspected adverse reaction.
An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

7.1.3 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

Unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. [4]

With these events the following will occur:

- *Modification of inclusion or exclusion criteria to mitigate the newly identified risks*
- *Implementation of additional safety monitoring procedures*
- *Suspension of enrollment of new participants or halting of study procedures for enrolled participants*
- *Modification of informed consent documents to include a description of newly recognized risks*
- *Provision of additional information about newly recognized risks to previously enrolled participants*.

7.2 CLASSIFICATION OF AN ADVERSE EVENT

7.2.1 SEVERITY OF EVENT

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

7.2.2 RELATIONSHIP TO STUDY AGENT

All AEs will have their relationship to study agent or study participation assessed.
Evaluation of relatedness will consider etiologies such as natural history of the underlying disease, concurrent illness, concomitant therapy, study-related procedures, accidents, and other external factors.

The clinician's assessment of an AE's relationship to study agent is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event will be reported. All AEs must have their relationship to study agent assessed. In a clinical trial, the study product will always be suspect. To help assess, the following guidelines are used.

- **Related** – The AE is known to occur with the study agent, there is a reasonable possibility that the study agent caused the AE, or there is a temporal relationship between the study agent and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study agent and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study agent caused the event, there is no temporal relationship between the study agent and event onset, or an alternate etiology has been established.

7.2.3 EXPECTEDNESS

The primary investigator will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

7.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review of subject questionnaires.

Information to be collected on al AE or SAE includes event description, time of onset, clinician's assessment of severity, relationship to study product, and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as

baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The primary investigator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 14 days (for SAEs) after the last study intervention. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

7.4 REPORTING PROCEDURES

7.4.1 ADVERSE EVENT REPORTING

The IRB will receive notification of any UP, AE, or SAE within 24 hours of discovery by the primary investigator.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. The primary investigator will be responsible for notifying FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the investigator's initial receipt of the information.

7.4.2 REPORTING OF PREGNANCY

If it is discovered that a subject is pregnant, the subject will discontinue any interventions and continue in the study while continuing safety follow-up until the conclusion of her pregnancy.

7.5 STUDY HALTING RULES

Administration of the study agent will be halted when two SAEs determined to be related are reported. The primary investigator will inform the FDA of the temporary halt and the disposition of the study.

7.6 SAFETY OVERSIGHT & CLINICAL MONITORING

An independent medical expert (medical monitor) will advise the study investigator and monitor participant safety. The role of the Medical Monitor is to 1) Review all AEs on a regular basis throughout the trial; 2) be available to advise the investigators on trial-related medical questions or problems, and 3) evaluate cumulative participant safety data and make recommendations regarding the safe continuation of the study. The Medical Monitor will remain blinded throughout the conduct of the clinical trial unless un-blinding is warranted to optimize management of an adverse event or for other

safety reasons. Clinical site monitoring is conducted to ensure that the rights and well-being of human

subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

8 STATISTICAL CONSIDERATIONS

8.1 STATISTICAL HYPOTHESES

Primary Endpoint

$H_0: \mu_C = 0$; $H_1: \mu_C > 0$

- The null hypothesis is the absolute mean difference in the change from baseline to 30 days after the last treatment on the treatment arm as compared to the non-treatment arm is zero.
- The alternative hypothesis is the absolute mean change from baseline to 30 days after the last treatment on the treatment arm as compared to the non-treatment arm is greater than zero.

1. Let μ_C represent the absolute mean difference between the treated arm as compared to the non-treated arm in the difference in the number of ecchymoses from baseline to 30 days after the last treatment.

2. Let μ_C represent the absolute mean difference between the treated arm as compared to the non-treated arm in the difference in the size of ecchymoses from baseline to 30 days after the last treatment.

A Paired t-test will be used to analyze the primary endpoint. The results of the statistical analysis will be presented as an odds ratio with 95% Confidence intervals. A Shapiro-Wilk Test will be used to assess the normality of data.

8.3 ADDITIONAL SUB GROUP ANALYSIS

The primary and secondary endpoint will be analyzed based on age, sex, race/ethnicity or other variable such as subjects behavior (smoking, diet, handedness, exercise, etc..)

8.4 SAMPLE SIZE

N/A – Pilot Study

8.5 MEASURES TO MINIMIZE BIAS

ENROLLMENT/ RANDOMIZATION/ MASKING PROCEDURES

In order to avoid bias, the subjects will be randomized to receive treatment on either their left or right arm. All evaluators of pictures will be blinded as to which technique was used on which side. In order to avoid bias, the evaluator will not be the primary investigator.

To ensure only the clinical investigator performing the procedures and the study coordinator know

the assignment of arms, each subject will have an envelope assigned to them to be held by the study coordinator with the subject's name on the outside and the assignment on the inside. Only during treatments does the study coordinator allow the clinical investigator to see the inside of the envelope.

The skin biopsy samples will be coded to ensure blinded analysis.

9 ETHICS/PROTECTION OF HUMAN SUBJECTS

9.1 ETHICAL STANDARD

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and the ICH E6.

9.2 INFORMED CONSENT PROCESS

Informed consent is required for all participants. In obtaining and documenting informed consent, the investigator will comply with applicable regulatory requirements and will adhere to 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and ICH GCP. Prior to the written informed consent, the consent forms will be provided to the participants. Consent forms describing in detail the study agent, study procedures, and risks will be given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product.

The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants will have the opportunity to think about being a participant prior to agreeing to sign. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

9.3 PARTICIPANT AND DATA CONFIDENTIALITY

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Siperstein Dermatology Group Boynton research office. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Siperstein Dermatology Group research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Siperstein Dermatology's Boynton Beach research office.

9.3.1 RESEARCH USE OF STORED HUMAN DATA

Pictures and data collected under this protocol may be used in future publications. Access to stored pictures and data will be stored using codes assigned by the investigators. Data will be kept in password protected computers. Only investigators will have access to the samples and data.

10 DATA HANDLING AND RECORD KEEPING

10.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) will be entered into a 21 CFR Part 11-compliant data capture system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data

that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 2 years after the formal discontinuation of the clinical study. These documents will be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.3 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. It is the responsibility of the site to use continuous vigilance to identify and report deviations within 7 working days of identification of the protocol deviation, or within 7 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to the IRB and sponsor. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

11 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial.

12 REFERENCES

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2. https://osp.od.nih.gov/clinical-research/clinical-research-policy
3. FDA Guidance for Clinical Investigators, Sponsors, and IRBs, Adverse Event Reporting to IRBs – Improving Human Subject Protection
   - FDA: Regulations Relating to Good Clinical Practice and Clinical Trials
   - *HHS: The HIPAA Privacy Rule*
   - ICH Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance
   - OHRP: Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events
   - OHRP: Human Subject Regulations Decision Charts
   - OHRP: Informed Consent Checklist
   - OHRP: IRBs and Assurances
   - OHRP: Policy & Guidance Index

- OHRP: Vulnerable Populations
- OHRP: Tips on Informed Consent
- 21 CFR Part 11: Electronic Records, Electronic Signatures
- 21 CFR Part 50: Protection of Human Subjects
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