NCT05027282

Clinical Study Protocol

A Prospective Study Evaluating the Safety and Effectiveness of the CLEAR + BRILLIANT TOUCH® diode laser 1440-nm and 1927-nm Combination Wavelength Treatment

Protocol Number: V01-CBT-401

Sponsor

Bausch Health Americas, Inc.
400 Somerset Corporate Boulevard
Bridgewater, NJ 08807
Main Office: (908) 927-1400

Sponsor Contact: [redacted]
Sr. Clinical Trial Manager

Protocol Version / Date:

Version 1.0, 04/07/2021
Version 2.0, 06/22/2021
Version 3.0, 09/13/2021

The study will be conducted according to the protocol and in compliance with EN ISO 14155:2020 Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practices, International Conference of Harmonization Good Clinical Practice Guidelines and all other applicable regulatory requirements and standards.

The Sponsor, Bausch Health Americas, Inc., is funding this clinical investigation.

Protocol Review and Approvals

Study Administrative Structure

Study Title: A Prospective, Study Evaluating the Safety and Effectiveness of the CLEAR + BRILLIANT TOUCH® diode laser 1440-nm and 1927-nm Combination Wavelength Treatment

Medical Monitor

[redacted]

Contract Research Organization (CRO)

SGS Stephens, Inc
Cheryl Vaughan, Clinical Investigator
SGS Stephens, Inc.
1801 North Glenville Drive
Richardson, TX 75081

Canfield Scientific, Inc

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4 Wood Hollow Road
Parsippany, NJ 07512
Imaging

ProPath

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Dallas, TX 75247
Biopsy sample analysis

Investigative Clinical Site[1]

[redacted]
Dallas Center for Dermatology and Aesthetics
8201 Preston Road #350
Dallas, TX 75225

[1] All contractual and financial agreements between clinical site and the Sponsor will be administrated by the Sponsor and approved at a minimum by both Investigators and the Sponsor in writing.

Principal Investigator Protocol Agreement Page

(PROTOCOL V01-CBT-401, DEVICE: CLEAR + BRILLIANT TOUCH® LASER SYSTEM)

COMMITMENTS OF THE INVESTIGATOR:

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after being notified by the Sponsor, except when necessary to protect the safety, rights, or welfare of subjects. I agree to comply with all requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 812.

I agree to personally conduct or supervise the described investigation(s). I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are adequately trained and qualified to fulfill their responsibilities and are informed about their obligations in conducting the study.

I agree to inform any patients, or any persons used as controls, that the device(s) are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

I agree to report to the Sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR Part 812.150.

I agree to disclose to the Sponsor accurate financial information to allow the Sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR Part 54. I agree to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.

I agree to maintain adequate and accurate records in accordance with 21 CFR 812.140 and to make those records available for inspection in accordance with 21 CFR 8 Part 12.145 and if I transfer custody of the records to any other person, I will notify the Sponsor.

I will be responsible for the control of devices under investigation and will ensure that the investigational device is used only with subjects under my supervision. Upon completion or termination of the clinical investigation, I will either return all investigational devices to the Sponsor or dispose of the device as instructed by the Sponsor.

I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to report to the IRB all deviations in the research activity and all unanticipated problems involving risks to human subjects or others, per IRB requirements. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

I have never been disqualified as an Investigator or had a research study terminated by the FDA, IRB/IEC or a Sponsor for noncompliance of an investigator agreement, investigational plan, IRB/IEC requirements or the requirements of 21CFR Part 50, 21 CFR Part 54, 21 CFR Part 56, CFR Part 312, or 21 CFR Part 812. If an investigation or other research was terminated, I will provide an explanation of the circumstances that led to termination.

A current Curriculum Vitae has been provided to the Sponsor to demonstrate education, training, and experience that qualifies me to conduct clinical research as an expert in the field related to the device under investigation.

[redacted]

LIST OF ABBREVIATIONS

ABBREVIATION/TERM	DEFINITION
AE	Adverse Event
CFR	Code of Federal Regulations
CRF	Case Report Form
EDC	Electronic Data Capture
EOS	End of Study
FDA	Food and Drug Administration
FDF	Financial Disclosure Form
GAIS	Global Aesthetic Improvement Scale
GCP	Good Clinical Practice
ICF/ICD	Informed consent form/ Informed consent document
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent To Treat
IQIS	Investigator Quartile Improvement Score
MTZ	Microthermal treatment zone
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
QHS	Every Night At Bedtime
SAE	Serious Adverse Event
UADE	Unanticipated Adverse Device Effect
UV	Ultraviolet
VAS	Visual Analog Scale

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1. STUDY SYNOPSIS

Name of Sponsor/Company	Bausch Health Americas, Inc.
Name of Device	CLEAR + BRILLIANT TOUCH® diode laser 1440-nm and 1927-nm
Title of Study	A Prospective, Single-Center Study Evaluating the Safety and Effectiveness of the CLEAR + BRILLIANT TOUCH® diode laser 1440-nm and 1927-nm Combination Wavelength Treatment.
Number of Clinical Centers	Single Center
Study Design	This is a prospective study of up to 30 subjects designed to assess the safety and effectiveness of a non-ablative fractional laser combination wavelength treatment for general resurfacing of photoaged skin. All study subjects will be treated on the whole face with the CLEAR + BRILLIANT TOUCH® 1440-nm and 1927-nm handpieces. Subjects will be treated with a consecutive series of four (4) treatments spaced 1 month apart, along with follow-up study visits at one (1) and three (3) months after final treatment.
Study Population	To be eligible for the study, the subjects must have mild (I) to moderate (II) photoaging by Glogau Photodamage Scale, no more than fine wrinkles and mild elastosis by Fitzpatrick Wrinkle and Elastosis Scale (Class I-II, Score 1-6). Both males and females will be considered, between the ages 18 and 65 years and Fitzpatrick skin Types I-VI with 70% skin types I-III and 30% skin types IV-VI. Number of subjects: Up to 30 subjects who meet all study inclusion/exclusion criteria will be considered for entry.
Study Objective	The objective is to evaluate the effectiveness and safety of the CLEAR + BRILLIANT TOUCH® diode laser combination treatment of 1440-nm and 1927-nm.
Study Endpoints	<u>Primary Effectiveness Endpoint:</u> improvement in the appearance of at least one measurement of photoaging damage (fine wrinkles, skin texture, dyschromia/pigment, skin radiance, pore size or overall appearance) by the investigator using the quartile improvement score comparing standard 2D baseline photograph captured via Canfield VISIA CA system and the 3 months post final treatment photograph. Reported percent change in improvement. <u>Secondary Effectiveness Endpoint:</u> improvement in the appearance of at least one measurement of photoaging damage (fine wrinkles, skin texture, dyschromia/pigment, skin radiance, pore size and overall appearance) by the investigator using the quartile improvement score comparing standard 2D baseline photograph captured via Canfield VISIA CA system to 1 month post final treatment photograph. Reported percent change in improvement. <u>Safety:</u> - Serious Adverse Events (SAEs) related and unrelated to the treatment procedure or to the CLEAR + BRILLIANT TOUCH® diode laser system. - The severity of post-treatment skin responses: • Immediate post-treatment erythema and edema. • Prolonged post-treatment erythema, edema, dryness/flakiness, hypopigmentation, hyperpigmentation, blistering, scarring. - The evaluation of pain and discomfort immediately after the treatment (within 60 minutes) as reported by the subject on a visual analog scale (VAS)

Exploratory Endpoints	Subject Modified Global Aesthetic Improvement Scale (GAIS) comparing their overall appearance in photos at 3 months post treatments with baseline photos. Subject Satisfaction with procedure recorded at 3 months post treatments. Five (5) patients will have 3 punch biopsies from an area of photoaging comparing baseline to 14 days and 3 months post treatments (location on the face at discretion of investigating physician either pre-auricular or at temple hairline. If face location unattainable the forearm exposed to photoaging may be used as an alternate biopsy location). Blinded Investigator: analysis of unmarked 2D photo sets via Canfield clinical system. Reviewers will select the order of baseline and post treatment one-month photos. Then based on their selection assess photos for percentage improvement in photoaging damage using the quartile improvement scale and score 0-4. Reported percent change in improvement of correct order sets. Blinded Investigator: analysis of unmarked 2D photo sets via Canfield clinical system. Reviewers will select the order of baseline and post treatment three-months photos. Then based on their selection assess photos for percentage improvement in photoaging damage using the quartile improvement scale and score 0-4. Reported percent change in improvement of correct order sets.

2. INTRODUCTION: BACKGROUND INFORMATION

Skin is susceptible to aging, much like all the other organs of the body. There are two different processes at work that lead to skin alterations. Intrinsic aging is a chronological, biological progression of degenerative changes associated with time, gravity, hormones, and genetics. Exposure to environmental factors contributes significantly to the aging process of the skin. The second process called extrinsic aging is a direct consequence of external elements, mainly induced by chronic exposure to ultraviolet (UV) radiation, and hence called photoaging.[3] UV changes vary considerably among different Fitzpatrick skin types and ethnicity.[1]

Extrinsic aging occurs in habitually exposed areas of the body such as face, neck, chest, and arms. Alterations in the skin from photoaging include uneven pigmentation, telangiectasia, wrinkles, roughness (textural changes), and occur in both the epidermis and dermis.[2] Histologically damage to the skin's dermal connective tissue occurs because of the loss of collagen, elastosis, and alterations of components in the extracellular matrix.[1] Increased and uneven pigmentation in photoaging are mostly a result of changes in melanocytes located in the basal epidermal layer.[7]

Patients seek out treatment options for both intrinsic and extrinsic skin concerns for general skin resurfacing. Laser treatments for photoaging began with ablative CO_2 (10,600 nm) lasers, which vaporized the epithelium and heated the dermis. These treatments had prolonged downtime and an increased risk of side effects. Non-ablative lasers were created to spare the epidermis and stimulate collagen in the dermis; they had a better safety profile; however, efficacy was limited.[3]

Non-ablative fractional lasers utilize different wavelengths to ablate or coagulate tissue in columns or microthermal treatment zones (MTZs). Tissue is not vaporized and the stratum corneum remains intact.[6] The skin then heals from both the edge of the wound and underlying tissue. The dermis undergoes necrosis leaving a dead space to be filled with new collagen and repair of tissue related to photoaging.[4] The spared areas shortened downtime and presented a smaller range of side effects, increasing the safety profile. Fractional resurfacing treatments utilizing multiple wavelengths in a single session over a series of treatments has clinical benefits for treating superficial and underlying dermal effects associated with photodamage.[5]

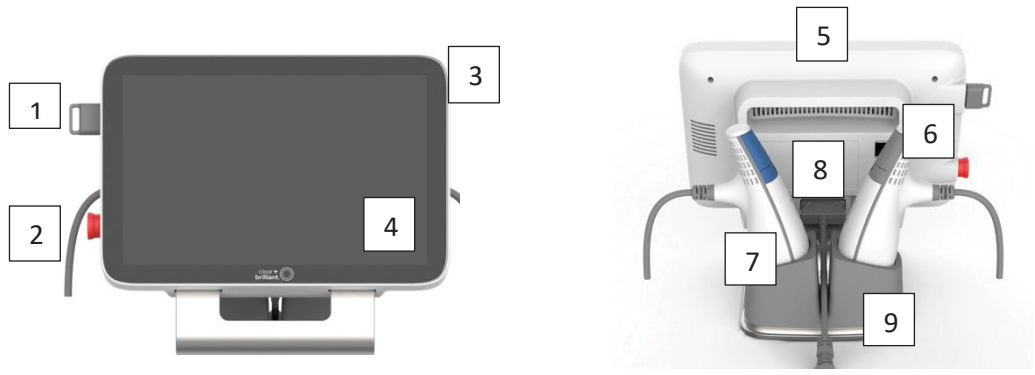
The CLEAR + BRILLIANT TOUCH® diode laser is a low powered and low density (0.9- 2.5 watt) non-ablative fractional diode laser that targets water as its chromophore. The system utilizes the principle of fractional photo thermolysis which means only limited areas of the skin are exposed to laser optical energy at one time. Healing time is minimized because the fractional photo thermolysis laser affects only a pre-determined percentage of the skin surface at any one time and does not cause full epidermal wounds. It can deliver a 1927 nm (170 µm fixed depth) and 1440 nm (280-390 µm depth) wavelength depending upon the handpiece desired while using the same credit key during a session.[8,9]

In this study, the effect and safety of delivering two wavelengths in the same session treatment, over a series of four treatments addressing alterations of photoaging using the CLEAR + BRILLIANT TOUCH® fractionated diode laser, will be assessed.

2.1 Device Description

The CLEAR + BRILLIANT TOUCH® System is manufactured by Solta Medical, Inc. (11720 North Creek Parkway N., Suite 100, Bothell WA 98011, USA) and is indicated for use in dermatological procedures requiring the coagulation of soft tissue and general skin resurfacing procedures. The CLEAR + BRILLIANT TOUCH® System consists of a console and two versions of the laser handpiece. The console connects to the facility power source and the handpieces produce laser energy delivered through removable, disposable treatment tips. A credit key is required to activate treatments and is inserted into the side of the console. Additional details on the CLEAR + BRILLIANT TOUCH® System can also be found in the CLEAR + BRILLIANT TOUCH® Laser System User Manual Revision D provided by the Sponsor.

The system includes the Original Handpiece (1440 nm) and the Perméa™ Handpiece (1927 nm), allowing for targeted treatment of different tissue depths.



Front and Rear view of the system

	Control/Connection/Description	Function
1	Credit Key	Contains treatment credits. Credit Keys are removable and are to be disposed of when finished.
2	Emergency Stop Switch	Stops the laser treatment beam when pressed during an emergency. To restart, twist the button and release it from the latched *Off* position.
3	Console	Houses the electro-mechanical components that operate the system.
4	Touch Screen	Displays information on operating the system, including system status, progress of the self-test, instructions, and general messaging. The Touchscreen is interactive: Select by tapping the onscreen buttons.
5	Power Button	Powers on and off the system.
6	AC Power Inlet, Network Connection, and USB Ports	Connects the Console to the Power Cord. Used by Solta Medical Maintenance. Downloads Charting information and used by Solta Medical Maintenance.
7	Handpieces	Generate laser energy, and where the Treatment Tips are attached. Two Handpieces are available: The Original Handpiece (1440 nm) in gray, and the Perméa™ Handpiece (1927 nm) in blue.
8	Handpiece Connection Ports	Connect the Handpieces to the Console. Disconnect using the workable latches.
9	Cradle	Holds the Handpieces when they are not being used. Installed Handpieces need to be resting in the Cradle when the self-test runs during the initialization of the system. This is automatically controlled by the software.

2.1.1 Mechanical Specifications

Size	31.75cm (W) x 28.58cm (L) x 27.94cm (H) 12.5” (W) x 11.25” (H) X 11” (D)
Weight	Approximately 15.5LBS (7kg)
Power Cord length	3m (10ft)
Handpiece Cable length	2m (6.6ft)

2.1.2 Laser Safety Standards

The CLEAR + BRILLIANT TOUCH® System meets applicable electrical and laser safety standards (per IEC 60601 series and IEC 60825-1) for a Class 1C laser.

The CLEAR + BRILLIANT TOUCH® System contains a Class 1C laser, according to IEC/EN 60825-1 standards. The user and associated staff must take precautions to prevent direct exposure of laser energy to the eyes.

Handpiece Technical Specifications:

Original Handpiece (1440 nm)	
Equipment classification IEC 60601-1	Class 1
Handpiece	Type BF Applied Part
IEC 60825-1 Classification	Class 1C – Invisible Laser Radiation
Wavelength	1440 ± 20 nm; min:1420 max:1460
Maximum Power (average)	2.5 W
Maximum Pulse Energy	9 mJ
Maximum Pulse Width	3 ms
Pulse Repetition Rate	< 400 Hz

Perméa™ Handpiece (1927 nm)	
Equipment classification IEC 60601-1	Class 1
Handpiece	Type BF Applied Part
IEC 60825-1 Classification	Class 1C – Invisible Laser Radiation
Wavelength	1927 ± 20 nm; min:1907 max:1947
Maximum Power (average)	0.9 W
Maximum Pulse Energy	5 mJ
Maximum Pulse Width	5 ms
Pulse Repetition Rate	< 150 Hz

2.1.3 Study Device Accountability

The Investigator will be responsible for keeping current and accurate device accountability records. At various time points throughout the study and/or upon completion of the study, the Sponsor or Sponsor's representative will review and verify the Investigator's accountability records.

Credit Keys and disposable Treatment Tips are used to restrict access to the device to only authorized users. Laser light can only be produced by the system when a valid Credit Key with available treatment credits is inserted into the Console and a Treatment Tip is attached to the Handpiece. One Credit Key is loaded with 12 treatment credits. The Investigator will be provided with sufficient Credit Keys /Treatment Tips to provide treatment for subjects enrolled into the study. Credit Key lot number and Treatment Tip lot number will be recorded for each subject treatment on the CRF.

Following study completion, study devices must be returned to the Sponsor. The Sponsor will be responsible for complete study accountability, returns, and reconciliation of the returned devices at the conclusion of the study.

3. STUDY OBJECTIVE:

The objective is to evaluate the effectiveness and safety of the CLEAR + BRILLIANT TOUCH® diode laser combination treatment of 1440-nm and 1927-nm.

4. STUDY DESIGN AND ENDPOINTS

4.1 Description of Study Design:

This is a prospective, non-randomized study of up to 30 subjects designed to assess the safety and effectiveness of a non-ablative fractional combination laser wavelength procedure for general resurfacing of photoaged skin. All study subjects will be treated on the whole face with the with the CLEAR + BRILLIANT TOUCH® diode laser 1927-nm & 1440-nm handpieces. Subjects will be treated with a consecutive series of four (4) treatments spaced 1-month apart, along with follow-up study visits at one (1) and three (3) months after final treatment. As primary and secondary effectiveness endpoints aim to evaluate improvement in photoaging damage post-treatment as compared to baseline following treatment with the FDA-cleared CLEAR + BRILLIANT TOUCH® System, no control group will be utilized.

4.2 Study Endpoints

4.2.1 Primary Endpoint

Primary Effectiveness Endpoint: improvement in the appearance of any one or more measurement of photoaging damage (fine wrinkles, skin texture, dyschromia/pigment, skin radiance, pore size and overall appearance) by the investigator using the quartile improvement score comparing standard 2D baseline

photograph and the 3 months post final treatment photograph. Reported percent change in improvement.

4.2.2 Secondary Endpoint

Secondary Effectiveness Endpoint: improvement in the appearance of any one or more measurement of photoaging damage (fine wrinkles, skin texture, dyschromia/pigment, skin radiance, pore size and overall appearance) by the investigator using the quartile improvement score comparing standard 2D baseline photograph and the 1 month post final treatment photograph. Reported percent change in improvement.

4.2.3 Safety Endpoints

Serious Adverse Events (SAEs) related and unrelated to the treatment procedure or to the CLEAR + BRILLIANT TOUCH® diode laser.

The severity of post-treatment skin responses:

- Immediate post-treatment erythema and edema (Visits: 1 and or 2 if screening and treatment on same day, Visits 3, 4 and 5)
- Prolonged post-treatment erythema, edema, dryness/flakiness, hypopigmentation, hyperpigmentation, blistering, scarring. (Visits 6 & 7)

The evaluation of pain and discomfort immediately after the treatment (within 60 minutes) as reported by the subject on a visual analog scale (VAS).

4.2.4 Exploratory Endpoints

i. Subject Modified Global Aesthetic Improvement Scale (GAIS) comparing their own photos at 3 months post treatments compared to baseline photos.
ii. Subject Satisfaction with procedure recorded at 3 months post treatments.
iii. Five (5) patients will have 2-mm punch biopsies from area of photoaging comparing baseline to 14 days and 3 months post treatments (location on face at discretion of investigating physician: either pre-auricular or at temple hairline. If face location is unattainable, the forearm, exposed to photoaging may be used as an alternate biopsy location). Pre- and post-treatment biopsies must be taken from the same general location for each patient.
iv. Blinded Investigator: analysis of unmarked 2D photo sets via Canfield clinical system. Reviewers will select the order of baseline and post treatment one-month photos. Then based on their selection assess photos for percentage improvement in photoaging damage using the quartile improvement scale and score 0-4. Reported percent change in improvement of correct order sets.
v. Blinded Investigator: analysis of unmarked 2D photo sets via Canfield clinical system. Reviewers will select the order of baseline and post treatment three-months photos. Then based on their selection assess photos for percentage

improvement in photoaging damage using the quartile improvement scale and score 0-4. Reported percent change in improvement of correct order sets.

5. INVESTIGATOR SELECTION AND STUDY POPULATION:

5.1 Investigator Selection

Investigators will be qualified based on professional experience in the diagnosis and treatment of photoaged skin including fine and coarse wrinkles, dyspigmentation, loss of tone, texture and elastosis using energy-based devices including lasers.

Investigators should be familiar with the risks and benefits described in Section 9. Investigator training and experience will be determined by the Sponsor to be suitable based on the Investigator's medical training and licensure.

5.2 Number of Participants

Up to 30 subjects who meet all study/exclusion criteria will be considered for entry.

Application of the inclusion and exclusion criteria in the following sections will result in the selection of an investigational population which is approximately representative of the intended target population.

5.3 Inclusion Criteria

Subjects must meet all the following inclusion criteria.

1. Male or female.
2. 18 to 65 years of age.
3. Written and oral informed consent must be obtained.
4. No more than Mild (I) to Moderate (II) classification on Glogau Photodamage Scale.
5. Fitzpatrick skin types I-VI.
6. Fitzpatrick wrinkle & elastosis scale class I-II, score 1-6 (fine wrinkles and mild elastosis).
7. Ability to read, understand and sign the informed consent form.
8. Agree not to take any new medications (unless prescribed by the study investigator) or undergo any other procedures that may potentially treat photodamaged skin (any other aesthetic treatments) during the study.

5.4 Exclusion Criteria

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

1. Pregnant, breastfeeding, or planning to become pregnant during the study.
2 History of any type of allergic reaction to lidocaine.
3. Recent and/or active localized or systemic infections.

4. Diagnosis/possibility of actinic keratosis, melasma, rosacea, or other significant skin conditions (e.g. skin cancer, active infections, cold sores, open wounds, rashes, burns, inflammation eczema, psoriasis).
5. Predisposition to keloid formation or excessive scarring.
6. Diagnosis of a condition that may compromise the immune system, such as: HIV, lupus, scleroderma, and/or systemic infections.
7. Known sensitivity to light or photosensitizing agents/medications are being taken.
8. Systemic steroids (e.g. prednisone, dexamethasone), which should be rigorously avoided prior to and throughout course of the treatment.
9. Use of retinoids less than 2 weeks prior to or during the study to completion.
10. Individuals undergoing Accutane™ treatment or drugs in a similar class.
11. Having skin that is still recovering from a cosmetic procedure: such as a chemical peel, or mechanical peel, or laser resurfacing within the previous 6 months.
12. Having had Botox injections, neurotoxin injections, or dermal fillers (such as collagen) within the past four months.
13. Sunburn and/or recent sun exposure on the treatment area in the last 2 weeks.
14. Subjects must agree to seek the advice of their medical doctor regarding any known or suspicious skin condition before laser treatment.
15. Any condition or situation that would prevent the subject from safely completing all protocol requirements for participation.
16. Subjects who are unable to communicate or cooperate with the investigator due to language problems, poor mental development, or impaired cerebral function.

5.5 Strategies for Recruitment and Retention

The recruitment process planned for this study will include any of the following scenarios:

- An individual voluntarily schedules an appointment at the physician's office (that in the context of this study also functions as the investigator's test site) relating to the treatment of photoaging.
- The study population may also be drawn from the investigator's existing database of subjects who have expressed an interest in treatment of photoaging.
- During the visit, if the physician perceives the subject may satisfy the study qualification criteria, the physician will present to the subject the option of being a subject in the study.
- If the subject is interested in possibly taking part in the study, the physician – now in the role of study investigator – will personally review the informed consent form with the individual and answer any questions. The individual may sign the informed consent form at that visit or he or she may think about it for a while and sign the informed consent form later. No timeline may be set for the subject to sign the consent form. Furthermore, the subject can refuse to participate in the study.
- An individual who decides to sign the consent form and proceed with participation in the study will receive a subject ID and proceed to the study qualification phase.
- Treatment will include a screening visit, four treatment visits and two follow up visits; a total of seven office visits to complete participation. (Screening visit and first treatment may be on same day if no biopsy is taken.) Biopsy patients will have a total of eight office visits to include an additional biopsy collection at 14 days post treatment #1 for enrollment completion.

5.6 Subject Enrollment

A subject is considered enrolled in the study at the time of the first treatment (Treatment #1) following confirmation of eligibility according to inclusion/exclusion criteria at the Screening Visit and again at Visit 2 (Treatment #1).

5.7 Subject Screen Failures

A subject who fails to meet eligibility criteria or discontinues from the study of their own volition before the first treatment will be considered a screen failure.

5.8 Subject Completion

The subject has completed the study when he/she completes Visit 7 (3-month follow-up). A subject who has missed visits or is missing study measurements will remain in the study. Subjects who require further follow-up for an adverse event (AE) or adverse device effect (ADE) will be followed according to Section 8.2. The same standard of care will be available for subjects who complete the study as for discontinued subjects (see Section 5.9) if such additional care is necessary because of the subjects' participation in the clinical investigation and where it differs from that normally expected for the medical condition in question.

5.9 Subject Discontinuation

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 reason for study withdrawal will be indicated on the study exit case report form. Every effort should be made to contact subjects lost to follow-up, and all such efforts should be documented in the subject's file.

If the subject withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations will be performed, and no additional data will be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent.

5.9.1 Reason for Withdrawal or Termination

A study subject will be discontinued from participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, intercurrent illness, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject.
- The subject meets any exclusion criteria (either newly developed or not previously recognized).

Subjects who are withdrawn will not be replaced.

5.9.2 Handling of Subject Withdrawal or Termination

If a subject voluntarily withdrawals, they will not be asked to continue the scheduled evaluations due to the short study duration. If subject is withdrawn from study because of adverse events they will be provided with the appropriate care under medical supervision.

6. STUDY PROCEDURES AND SCHEDULE:

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 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 these subjects' files and copies will be provided to the subjects. The informed consent process must be followed, and the subjects' participation in the study must be documented in the subjects' medical record/CRF.

6.2 Pre-Procedure

Study subjects will have verification of eligibility criteria, a brief general examination including medical history, vital signs and pre-procedure assessments as detailed below, completed within 30 days prior to undergoing the study procedure. Up to two urine pregnancy tests must be obtained prior to study procedure for females with childbearing potential (one at pre-procedure screening and one on the day of the procedure prior to the procedure if the pre-procedure screening and procedure are not performed on the same day).
The following pretreatment assessments will be performed:

- Standard 2D photographic images will be captured via the Canfield Scientific Inc, VISIA CA imaging system. The same standardized photography views (right, left, front facing) will be used throughout the study as documented in the image capture document developed for the study.
- Urine pregnancy test for females of childbearing potential; any premenopausal female capable of becoming pregnant. (Excluded: Non-childbearing potential, i.e. post-menopause, bilateral tubal ligation, oophorectomy, hysterectomy)
- Abbreviated general physical exam including medical history, vital signs, collection of subject's demographic information, Glogau photodamage assessment, Fitzpatrick skin type, Fitzpatrick Wrinkle and Elastosis Scale. (Appendixes A, B, C respectively)

Medications the subject is taking upon entry into the study should also be documented in the case report forms. Documentation should include medications that study subjects take on an elective basis in addition to prescribed medications.

After confirming fulfillment of all inclusion and exclusion criteria, the subject will be scheduled to undergo a CLEAR + BRILLIANT TOUCH® 1440-nm and 1927-nm combination wavelength treatment.

Patient Pre-treatment instructions:

- Skin types IV-VI: Begin Hydroquinone 8% QHS at discretion of treating physician, 2-3 weeks prior to first treatment. Hold while skin is healing between treatments, then restart QHS or as directed.
- Wash face with CeraVe® cleanser.
- Do not apply any topical facial products the morning of your treatment.
- Do not wear jewelry.
- Hair pulled back.
- Bring a hat to wear that shields from the sun.
- Bring on day of treatment the sponsor provided CeraVe® moisturizer and SPF to apply after treatment.

6.3 Study Procedure

During the study procedure, subjects will be treated with the CLEAR + BRILLIANT TOUCH® diode laser device combination wavelength 1440-nm and 1927-nm treatment.

Perform pattern preview test prior to use of device.

1. First the face will be cleansed with alcohol, topical anesthetic of 7% Lidocaine/7% Tetracaine will be applied 30 minutes prior to treatment.
2. Prior to treatment, the anesthetic will be fully wiped off and then face is cleaned again with rubbing alcohol to ensure face is free of all moisture and water. Allow to dry.
3. Provide patient protective eyewear. (Disposable or Non-disposable laser eye shields). Laser goggles for staff. With appropriate protection range for the system laser wavelengths (1440 nm ± 20 nm and 1927 ± 20 nm) and optical density of 5 or greater.
4. Attach single-use treatment tip.
5. Pre-set for 3200 cm^2 treatment area coverage or Time: 40 minutes.
6. Full face will be treated with 4 passes of the 1440-nm Original handpiece on high setting for all skin types I-VI, with two passes in the horizontal direction and two passes in the vertical direction (Fig A.) in each treatment zone (Fig B, C). *(Adjustments may be made to lower setting for patient tolerance)*

Fig. A

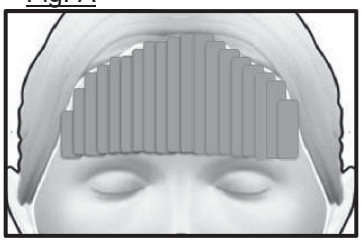


Fig. B

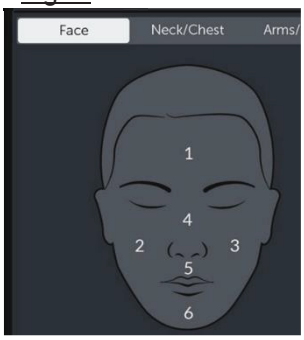
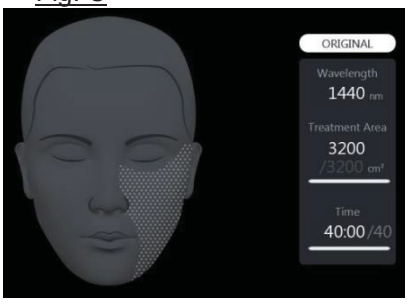


Fig. C



7. Full face will be treated with 4 passes of the 1927-nm Perméa on high setting for all skin types I-VI, with two passes in the horizontal direction and two passes in

the vertical direction in each treatment zone. *(Adjustments may be made to lower setting for patient tolerance)*

8. The total is a combined 8 passes in each treatment zone.
9. CeraVe® moisturizer and SPF 30+ to be applied to entire face immediately after treatment.

6.4 Follow-up Procedure

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

Post Care and Instructions:

1. Wash face with CeraVe® gentle cleansing product only.
2. Do not use an abrasive cleanser or brush device to clean face.
3. Apply CeraVe® moisturizer minimum twice a day while skin is healing and then as needed.
4. SPF 30+ daily. (approved by investigator)
   Sun exposure before and during treatment can increase the risk of unwanted pigmentation. After treatment the skin is more sensitive to the sun, which can increase the risk of unwanted pigmentation and sunburn. Post-treatment individuals should plan to use a high SPF sunscreen on a regular basis whenever they are outside. Ideally, a dual UVA/UVB sunscreen should be applied containing both a physical sun block (either or both zinc oxide or titanium dioxide) with a sun protection factor of 30 or above. Applying sunscreen helps maintain good results. In general, it is recommended that direct sunlight is avoided and to wear sun-protective clothing (i.e. a wide-brimmed hat) when possible.
5. Schedule next appointment.
6. Review and dispense the Subject home diary for post treatment skin effects.
7. For patients on the 8% hydroquinone therapy (Skin types IV-VI) hold this application while skin is healing, then restart QHS or as directed.

Subjects will be asked to return to the study site for subsequent procedures and post treatment follow up.

Post procedure Standard 2D images will be captured via the Canfield Scientific Inc, VISIA CA imaging system during the follow-up visits.

6.5 Data Collection

Subject demographic information, procedural data, adverse events, treatment observations and study required assessments will be documented on the case report forms (CRFs). Study subjects will complete satisfaction and modified global aesthetic improvement scale evaluations at the 3-month follow up. The Investigators will assess post treatment skin effects immediately post treatment, at follow up visits (prolonged post treatment) and quartile improvement scores at one (1) month and three (3) months in comparison to baseline photography. Blinded Investigators will provide analysis of unmarked 2D photo sets via Canfield clinical system. Reviewers will select the order of baseline and post treatment at one (1) month and three (3) months. Then based on their selection assess photos for

percentage improvement in photoaging damage using the quartile improvement scale and score 0-4.

6.5.1 Photography

VISIA CA facial photography system and services will be provided by the photography vendor, Canfield Scientific, Inc. (Parsippany, NJ) to document treatment effect from baseline to follow up visits. The camera system standardizes the facial (front, left and right oblique) images captured and lighting modalities.

All consenting subjects' study photographs will be captured using the equipment, supplies, and guidelines provided by Canfield to have consistent visual representation of the facial appearance during the study treatment.

Images will be captured, viewed, and uploaded using Canfield Clinical Services website which automatically checks, sums, encrypts, packages, and transfers the data to a secure, validated and compliant web server hosted by Canfield. Only approved individuals by the Sponsor have access to the study database on the website.

Detailed instructions for all aspects of the photography procedures will be supplied separately in the investigator user manual to be provided by Canfield. Images will be utilized for study research purposes (add other purposes, analysis if applicable).

6.5.2 Specimens

Five patients who provide additional consent to provide biopsies will have three (3) punch biopsies taken by the Investigator or site designee in the treatment area (area of photodamage). Location of biopsies will be pre-auricular, at temporal hairline, or the forearm. Pre- and post-treatment biopsies must be taken from the same general location for each patient.

- The first biopsy will be collected at Screening/Baseline visit (pre-Treatment #1) The first treatment will be subsequently scheduled at the discretion of the principal investigator as they determine the biopsy site to be healed for treatment.
- The second biopsy will be collected at 14 days following the first treatment. The second treatment will be subsequently scheduled at the discretion of the principal investigator as they determine the biopsy site to be healed for treatment.
- The third biopsy will be collected at 3-month follow up (3-months post final treatment, Treatment #4).

6.6 Final Study Visit

Three-month 2D follow-up photographs will be taken captured via the Canfield Scientific Inc, VISIA CA imaging system.

Subjects will complete satisfaction surveys and GAIS overall improvement scores.

Investigators will complete Quartile Improvement Scales comparing baseline photography to 3 months photography.

6.7 Study Completion

The Sponsor or its representative will notify the Investigator and/or the IRB, as applicable, to inform them when the study is complete. The study will be considered complete when all enrolled subjects either have completed study visits through Visit 7 (3-month follow up) or have been discontinued from the study prior to Visit 7 for any reason.

6.8 Schedule of Events Table

Schedule of Events

	VISIT 1	**VISIT 2**	**VISIT 2a**	**VISIT 3**	**VISIT 4**	**VISIT 5**	**VISIT 6**	**VISIT 7**
PROCEDURES	**Screening Visit (Day -30 to 0)**	**Treatment #1 (Baseline)**	**Day 14 Biopsy** (14 days post treatment #1, +/- 7 days)	**Treatment #2** (1-month post treatment #1, +/- 7 days)	**Treatment #3** (1-month post treatment #2, +/- 7 days)	**Treatment #4** (1-month post treatment #3, +/- 7 days)	**1-Month F/U** (1 month post final treatment, +/- 7 days)	**3-Month F/U** (3 months post final treatment, +/- 7 days)
Informed Consent/Photo Release	X							
Demographics	X							
Medical History	X	X						
Vital Signs	X							
Concomitant Medications	X	X		X	X	X	X	X
Inclusion/Exclusion Criteria	X	X						
Previous Therapies	X	X						
Urine Pregnancy Test	X	X						
2D Standard Photography		X		X	X	X	X	X
Investigator Intake Assessments	X	X						
Punch Biopsy	X		X					X
Laser Treatment		X		X	X	X		
VAS Visual Analog Scale		X		X	X	X		
Side Effects Evaluation		X		X	X	X	X	X
Adverse Events Review	X	X		X	X	X	X	X
Investigator Quartile Improvement Evaluation							X	X
Prolonged Treatment Effects							X	X
Subject GAIS								X
Subject Diary[a]		X		X	X	X		
Subject Satisfaction								X
End of Treatment(s)						X		
End of Study								X

[a.] Subject's will log post-treatment skin responses, side effects (e.g., erythema, edema) using a scale of 0 to 3 (none to marked) after each treatment for seven (7) days in the subject diary.

Visit 1 (Day 0-30) Screening

A prospective subject is to be examined to determine if they qualify for entry into the study. This initial examination will include:

- Obtain written Informed Consent and photographic release
- Review Inclusion/Exclusion Criteria
- Record Medical History/Meds/Vital Signs
- Urine Pregnancy Test (if applicable): only one is necessary prior to start of treatments.
- Dispense CeraVe® Products
- Skin types IV-VI: Begin Hydroquinone 8% QHS at discretion of treating physician 2-3 weeks prior to first treatment. Hold while skin is healing, then restart QHS or as directed.
- Investigator Assessments: Glogau Photodamage, Fitzpatrick Skin Type and Wrinkle & Elastosis Scale
- Biopsy #1 of five patients (baseline)
  Note: Screening and Baseline visits may occur on the same day for non biopsy patients.

Visit 2 Baseline/Treatment #1 (Screening/Baseline may be on same day)

This treatment visit will include:

- Photographs prior to treatment: wait at least 15 min indoors, 2D standard photography captured via Canfield VISIA CA.
- Urine Pregnancy Test (if applicable): only one is necessary prior to start of treatments.
- Laser treatment to the face
- VAS Scale
- Post Treatment Skin effects (provider)
- Review for Adverse Events (provider)
- Subject Diary post treatment (7 days) given to patient.

Visit 2a Biopsy Patients Only (14 days post treatment #1, +/- 7 days)

- Biopsy #2 of selected five patients

Visit 3 Treatment #2 (one-month post treatment #1, +/- 7 days)

This treatment visit will include:

- Prior to treatment: wait at least 15 min indoors, 2D standard photography via Canfield VISIA CA
- Laser treatment to the face
- VAS Scale
- Post Treatment Skin effects (provider)
- Review for Adverse Events (provider)
- Subject Diary post treatment (7 days) given to patient

Visit 4 Treatment #3 (one -month post treatment #2, +/- 7 days)

This treatment visit will include:

- Prior to treatment: wait at least 15 min indoors, 2D standard photography via Canfield VISIA CA
- Laser treatment to the face
- VAS Scale
- Post Treatment Skin effects (provider)
- Review for Adverse Events (provider)
- Subject Diary post treatment (7 days) given to patient

Visit 5 Treatment #4 (one-month post treatment #3,+/- 7 days,)

This treatment visit will include:

- Prior to treatment: wait at least 15 min indoors, 2D standard photography via Canfield VISIA CA

- Laser treatment to the face
- VAS Scale
- Post Treatment Skin effects (provider)
- Review for Adverse Events (provider)
- Subject Diary post treatment (7 days) given to patient

Visit 6 Follow-Up Visit (one-month post treatment #4, +/- 7 days)

This follow-up examination will include:

- Photography: wait at least 15 min indoors, 2D standard photography via Canfield VISIA CA
- Prolonged Post Treatment Skin effects
- Review for Adverse Events
- Investigator Quartile Percent Improvement Evaluation

Visit 7 Follow-Up Visit (three months post treatment #4, +/- 7 days)

This follow-up examination will include:

- Photography: wait at least 15 min indoors, 2D standard photography via Canfield VISIA CA
- Prolonged Post Treatment Skin effects
- Review for Adverse Events
- Subject GAIS and satisfaction
- Investigator Quartile Percent Improvement Evaluation
- Biopsy #3 of selected five patients

7. EVALUATION TOOLS

7.1 Investigator Evaluation Standard 2D Photography

Two-dimensional (2D) facial photographic images will be captured by the Canfield Scientific, Inc. VISIA CA imaging system.

- The camera system standardizes the facial (front, left and right oblique) images captured and lighting modalities.
- All makeup should be removed, hair pulled back in consistent manner and behind the ears, all jewelry removed.
- Patients will be notified in their informed consent about the collection and use of their photographs for research purposes which may be used for scientific, educational presentations or publications.

The data will be comparing baseline photos to 1- and 3-months post treatment for results.

7.2 Investigator Evaluations Quartile Improvement Score

Treating Investigators will compare:

1. Baseline photographs to one-month post treatment.
2. Baseline photographs to three-months post treatment.

A Quartile Improvement Scale will be used to individually score each category: (a) fine wrinkles, (b) skin texture, (c) dyschromia/pigment, (d) skin radiance, (e) pore size and (f) overall appearance.

Investigator Quartile Improvement Score		
Rating	Percentage (%)	Score
No Improvement	0%	0
Minor/Mild Improvement	1%-25%	1
Moderate Improvement	26%-50%	2
Marked Improvement	51%-75%	3
Very Significant Improvement	76%-100%	4

7.3 Punch Biopsies

Up to five (5) subjects will be consented to provide skin biopsies. Each subject will provide up to three (3) punch biopsies. 2 mm punch biopsies will be taken from the location on the face in an area of photoaging at discretion of investigating physician either pre-auricular or at temple hairline. If face location is unattainable the forearm (exposed to photoaging) may be used as an alternate biopsy location and will receive the combined laser treatment in addition to receiving a facial treatment. Pre- and post-treatment biopsies must be taken from the same general location for each patient.

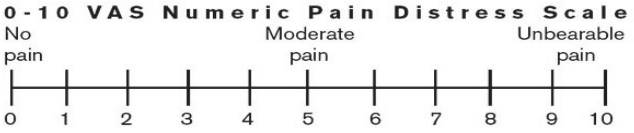
Biopsies will be obtained using standard sterile technique after an intradermal local anesthesia, closed with suture (at the discretion of the Sub-Investigator/Study Physician), and treated with topical antibiotic and sterile dressing in routine fashion. Subjects' skin may be marked with a surgical marker to use as reference. Complete anesthesia of the biopsy site will be confirmed prior to the punch being inserted.

The biopsies will be immediately transferred into 10% formalin solution and stored at room temperature. Collected biopsy samples will be sent to Propath for biopsy sample analysis. IHC staining for Procollagen I, elastin, CD31, lymphocyte count, Masson's trichrome, GAG (Colloidal/Fe), and H&E, with images. 15 samples total will be collected (5 sets at baseline, day 14 and final visit).

The biopsy sample manifest will be sent to Propath and will contain the subject number, product information, total number of biopsies collected, and any other relevant information needed to identify the samples post-analysis.

7.4 Visual Analog Scale (VAS)

The study subjects will be asked to complete an eleven point visual analog scale (VAS, 0-10) for the level of pain and discomfort associated with the study procedure to be completed by the subjects on the day of the procedure immediately after or within 60 minutes from the end of the procedure and recorded in the CRF treatment record. They may verbally respond with a numeric pain score.



Scoring will be reported by the provider on the treatment record.

7.5 Subject Satisfaction

Using a five (5) point Likert scale the study subjects will be asked to complete a satisfaction survey to rate their overall treatment results at the three-month follow-up visit.

Overall how would you rate your satisfaction with the treatment results?	Very Dissatisfied	1
	Dissatisfied	2
	Neither Satisfied nor Dissatisfied	3
	Satisfied	4
	Very Satisfied	5

7.6 Subject Modified Global Aesthetic Improvement Score

The Modified Global Aesthetic Improvement Scale (GAIS) is a subjective rating of improvement of treatment results compared to pre-treatment. The subjects will grade the overall improvement of the appearance of the treatment areas. The subject will compare their appearance at three months against a photograph taken at baseline.

SUBJECT MODIFIED GLOBAL AESTHETIC IMPROVEMENT SCALE	
Comparing baseline photograph to three-months photograph.	Rating
How do you rate your overall appearance compared to before treatment?	□ Very Much Improved
	□ Much Improved
	□ Improved
	□ No Change
	□ Worse
	□ Much Worse
	□ Very Much Worse

7.7 Independent Photographic Assessments

Two experienced, blinded photographic reviewers will compare 2D photographs via Canfield Scientific, Inc VISIA data access system:

1. The reviewer will select between 2 sets of unmarked photos and determine which is baseline and one-month post treatment. Based on their selection of baseline to one-month post treatment the reviewer will rate improvement.
2. The reviewer will select between 2 sets of unmarked photos and determine which is baseline and three-months post treatment. Based on their selection of baseline to three-months post treatment they will rate improvement.

A Quartile Improvement Scale will be used to individually score each category: (a) fine wrinkles, (b) skin texture, (c) dyschromia/pigment, (d) skin radiance, (e) pore size and (f) overall appearance.

Blinded Investigator Quartile Improvement Score		
Rating	Percentage (%)	Score
No Improvement	0%	0
Minor/Mild Improvement	1%-25%	1
Moderate Improvement	26%-50%	2
Marked Improvement	51%-75%	3
Very Significant Improvement	76%-100%	4

If the incorrect order is selected that grouping will not be used to calculate improvement. The percentage of correct to incorrect will be calculated for both one-month and three-month assessments.

8. ASSESSMENT OF SAFETY

8.1 Specification of Safety Parameters

- Post-treatment skin responses, side effects (e.g., erythema, edema) will be scored by the study investigators, as appropriate, using a scale of 0 to 3 (none to marked), immediately after treatment, for each treatment.
- Side effects (prolonged erythema, edema, skin darkening or lightening in the treatment area, scarring, dryness/flakiness, blistering) will be scored, using a scale of 0 to 3 (none to marked), by study investigators at the beginning of every subsequent treatment, and at all follow-up visits.
- Subject's will log post-treatment skin responses, side effects (e.g., erythema, edema) using a scale of 0 to 3 (none to marked), after each treatment for seven (7) days in the patient diary.
- In addition, study subjects will be instructed to report all 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 the procedure using the definitions below.

8.1.1 Definition of Serious Adverse Events (SAE)

<u>Serious Adverse Event (SAE) is an adverse event that:</u>

- 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 inpatient hospitalization or prolongation of existing hospitalization,
  - Resulted in medical or surgical intervention to prevent impairment to body structure or a body function, or
  - Lead to fetal distress, fetal death or congenital abnormality or birth defect.

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

8.1.2 Definition of Adverse Events (AE)

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 temporarily associated with the subject's participation in research whether or not considered related to the subject's participation in the research period.

A pre-existing 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.

8.1.3 Definition of Unanticipated Adverse Device Effect (UADEs)

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 a nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), 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.

8.1.4 Definition of Device Malfunction

Malfunction means the failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed, as defined in 21 CFR § 801.4.

8.2 Adverse Event / Device Malfunction Reporting

In the case of an AE (Serious and Significant Non-Serious) or UADE the Investigator must:

Report the AE or UADE to the Medical Monitor within 24 hours of knowledge of the event using the Sponsor-provided form (SAE/UADE reporting form, Appendix D) by emailing the completed form to the Medical Monitor [redacted]

The Medical Monitor will email/fax a copy of the form immediately (within 24 hours) for SAEs/UADEs only to [redacted] upon receipt.

In the case of Device Malfunctions, the Investigator must:

Report the Device Malfunction within 24 hours using the Sponsor-provided form (Device Malfunction reporting form, Appendix E) by emailing the completed form to [redacted]

All 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, unanticipated serious device related effect or device malfunction 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 the follow-up includes any supplemental investigations as may be indicated to elucidate, as completely 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 adverse events to the clinical study staff and information will be collected throughout the study and recorded on the case report forms and reported to Solta Medical Customer Service.

8.3 Classification 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 events are usually relieved by simple therapeutic measures.
- **Severe**: prevents normal everyday activities these events may require systemic drug therapy or other medical treatment.

8.4 Relationship to the study device and/or procedure

The causality assessment is a determination of the relationship between the investigational device or surgical procedure and the occurrence of an AE/SAE.

The possibility of a link between the study device or surgical procedure and an AE will take into consideration (as a minimum) the following criteria:

- Existence of a temporal link between the event and administration of the study device.
- Event is not explained by any other condition, measure or environmental factor.

For this study, causality will be defined as:

- **Related:** There is at least a reasonable possibility that the AE/SAE is related to the study device or surgical procedure. Reasonable possibility means that there is evidence to suggest a causal relationship or association between the study device and the AE. Also referred to as an ADE.
- **Unrelated:** There is little or no reasonable possibility that the AE/SAE is related to the study device or surgical procedure. This assessment implies that the AE/SAE has no evidence to suggest either a causal relationship or association to the study device or surgical procedure and more likely or certain an alternative etiology exists.

8.5 Termination of Study Rules for Safety

The Sponsor and/or Investigator may recommend termination or modification of the study if there is an occurrence of any device or treatment related Serious Adverse Event using the following clinical protocol definitions of Serious Adverse Event in section 8.1.1 of this protocol. In addition, termination, or modification may be recommended for any other perceived safety concern based on clinical judgment, including but not limited to a higher than anticipated rate for any component of the safety measures, device failures result resulting in Adverse Events or unexpected SAEs.

9. RISKS AND BENEFITS

9.1 Benefits

A possible benefit of using the CLEAR + BRILLIANT TOUCH® diode laser technology in a combination wavelength same session treatment, over a series of four treatments, is an enhanced improvement in the tone, texture, radiance, fine lines, pore size and overall appearance of the skin compared to no treatment at all.

9.2 Risks

9.2.1 Expected Responses

Clinical studies have shown that CLEAR + BRILLIANT diode laser treatments have a demonstrated safety profile. There is a very low incidence of side effects and complications associated with treatment. Risks and discomforts for subjects who participate in this study are the same as for subjects undergoing any dermatological laser treatment. Eye injury due to use of the laser system is a risk to the subject and the operator. Appropriate eye protection will be used to minimize that risk. Mild to moderate local pain is a typical reaction to laser treatments. Topical anesthetic will be applied prior to laser treatments. Eye injuries may result from numbing cream getting into the eyes. Eyes will be covered with protective eyewear during treatment and should remain closed during the treatment.

Expected Responses:

- Erythema (Redness)
- Edema (Swelling)
- Itching/Dryness
- Increased Skin Sensitivity
- Pain or Discomfort
- Pinpoint Bleeding/Petechia

9.2.2 Unexpected Responses

The following complications are very rare but may be associated with non-ablative laser treatments. This is not intended to be an all-inclusive list, nor a substitute for informed consent, which should be provided by every individual.

Complication	Description
Discoloration	The possibility of temporary and permanent skin color change is known to exist with any laser treatment. Post-inflammatory hypopigmentation and hyper-pigmentation are known complications of many laser treatments and may occur with CLEAR + BRILLIANT TOUCH® treatment. Following appropriate instructions for sun protection will lower the risk for pigmentation changes.
Infection	A risk of infection exists whenever the skin is wounded. The possibility for infection exists even with non-ablative fractional laser devices such as the CLEAR + BRILLIANT TOUCH® System. An infection should be treated appropriately with topical and/or systemic medications.
Prolonged Redness	Mild-moderate transient erythema is an expected response with any laser treatment. However, if erythema is severe or persists significantly longer than expected, re-treatment should be avoided until the condition resolves. Reaction may vary on a person-to-person basis.
Scarring	The possibility for scarring exists with any laser treatment, even with non-ablative laser devices such as CLEAR + BRILLIANT TOUCH® System. Local scarring may occur directly from laser exposure if treatment procedures are not followed properly, or from infection or physical irritation such as picking and rubbing.
Delayed Wound Healing/Skin Textural Changes	Following any laser treatment, re-epithelialization may not occur as expected due to an individual's physiology (i.e. poor wound healing ability, or post-treatment care). This may result in undesirable textural changes.
Temporary Bruising	Temporary bruising may develop over the treated areas and typically dissipates within several days.

9.2.3 Biopsy Risks

Skin Biopsy - There will be temporary discomfort when the local anesthetic is injected and when its effect wears off. Some slight bleeding may occur after the biopsy. There is a rare risk of infection. The biopsy may leave a small scar. The scar may be permanent.

9.3 Mitigation of Risks

These risks are mitigated by utilizing qualified clinical investigators who have training and are experienced in (1) performing energy based and laser procedures and (2) following study treatment procedures. In addition, risks are mitigated by including only those subjects that meet the study eligibility criteria. The study also includes evaluation of study subject satisfaction with this procedure. Given the anticipated acceptable risk, the risk benefit assessment of the use of the CLEAR + BRILLIANT TOUCH® diode laser device to improve the appearance of photoaged skin appears to offer a substantial clinical benefit at a reasonable risk.

Further discussion of risks of the of the CLEAR + BRILLIANT TOUCH® System can also be found and should be accessed in the CLEAR + BRILLIANT TOUCH® Laser System User Manual provided by the Sponsor.

10. STATISTICS

10.1 Statistical Analysis Populations and Demographics

The intent-to-treat (ITT) population will be the primary population for all statistical analyses. The ITT population will include all subjects who received treatment, participated in at least 1 post-baseline evaluation, and were not otherwise disqualified.

Subjects may be removed from the analysis in the case of an AE, SAE, noncompliance, or Investigator decision. The reason for any subject(s) excluded from an analysis population will be documented in a note to file and included in the study report.

Demographic data and baseline characteristics, including age, gender, ethnicity, Fitzpatrick skin type, Glogau rating, and Fitzpatrick wrinkle & elastosis scale rating, will be summarized according to the analysis population for all subjects. For continuous variables, descriptive statistics including number of subjects (N), mean, median, standard deviation (SD), minimum (MIN) and maximum (MAX) values will be presented. For categorical variables, the count and percentage of each category will be provided. The denominator for all percentages will be the number of subjects with non-missing data at the given visit for each respective study treatment, unless otherwise indicated.

The sample size determination of this study is based on the Sponsor's recommendations to quantify the effectiveness and safety of the CLEAR + BRILLIANT TOUCH® diode laser 1440-nm and 1927-nm Laser in the context of this study. Power calculations were performed based on estimates for expected mean change and variance in overall appearance at 3 months as rated by the Investigator using the Quartile Improvement Scale from study 12-133-CBP-F ('Evaluation of the skin after treatment with the Clear + Brilliant 1927-nm wavelength laser by means of the VISIA-CA Imaging System'). The power calculations demonstrated a sample size of 25 has greater than 95% power to reject the null hypothesis (change from baseline=0) for the primary efficacy endpoint. Thus, up to 30 subjects will be enrolled to account for potential drop-out.

10.2 Statistical Analysis Plan (SAP)

10.2.1 Descriptive Statistical Summary

A descriptive statistical summary will be provided for Investigator Quartile Improvement Score (IQIS, 0-4), tolerability parameters, VAS scores, and biopsy parameters. The descriptive statistical summary includes the N, mean, median, SD, MIN, and MAX of scores/values at all applicable time points.

Counts and percentages will be provided for Investigator Quartile Improvement Score (rating), SAE parameters, tolerability parameters, VAS (in category), and individual response data (GAIS and subject satisfaction).

10.2.2 Additional Analysis

Additional analysis will be provided as following:
For IQIS (0-4), the mean score will be compared to a constant value of 0 to test the null hypothesis that there is no improvement after the product use, using the method described in the SAP table.

For GAIS and subject satisfaction data, a binomial (sign) test will be performed to test if the proportion of the combined designated favorable responses (Very Much Improved, Much Improved, and Improved for GAIS; Very Satisfied and Satisfied for subject satisfaction) is equal to the combined designated unfavorable responses.

Statistical Analysis Plan Table

Evaluation	Change from baseline	Notes/Interpretation
Investigator Quartile Improvement Score	The mean score (0-4) will be compared to the constant 0, using Wilcoxon signed rank test	Significantly greater than 0 indicates improvement.
SAEs	NA	Zero or low number of SAEs is favorable
Tolerability parameters	NA	Lower score indicates better tolerability
VAS	NA	Lower score indicates better tolerability
Biopsy parameters	NA	Descriptive statistics only
Individual response data (GAIS and satisfaction)	NA	A binomial test (sign test) *P* value will be provided. A higher percentage of combined favorable responses with a significant *P* value indicates positive subject perceptions of the test material.
Blinded Investigators	The mean score (0-4) will be compared to the constant 0, using Wilcoxson signed rank test	Significantly greater than 0 indicates improvement.

All statistical tests will be 2-sided at significance level alpha=0.05 unless specified otherwise. *P* values will be reported to 3 decimal places (0.000).
No multiple testing corrections will be considered in the study. Statistical analyses are performed using SAS software version 9.4 (SAS Statistical Institute). The statistical results will be sent to the Sponsor along with raw data in a Microsoft Excel document at completion of the study.

10.2.3 Minimization of Bias and Potential Confounding Factors

Blinded investigator photo evaluation is intended to minimize bias.

11. SOURCE DOCUMENTS AND ACCESS TO DATA/DOCUMENTS

The PI shall supply the study monitor or IRB on request with any required background data from the study documentation or clinic records.

This clinical investigation will permit the investigator to proceed with “data entry” directly onto the case report forms (CRFs). In this case, the CRFs will also serve as the source record for each participating subject. A copy of the CRFs will be collected by SGS Stephen’s Inc. for data analysis.

12. QUALITY ASSURANCE AND QUALITY CONTROLS

Each investigational site will undergo a detailed training that highlights the key tenets for maintaining quality management. The investigational sites will be instructed regarding protocol compliance, use of CRFs, and proper treatment administration. The investigator must assure that subject confidentiality will be maintained and that participant identities shall be protected from unauthorized parties.

12.1 Study Monitoring

The Sponsor and its representatives must be allowed to visit the study site location to assess the data, quality, and study integrity.

Prior to the start of the study, member(s) of the Sponsor (or designees) will review the protocol, CRF, regulatory obligations, and other material or equipment relevant to the conduct of the study with the Investigator and relevant study site personnel.

Monitoring visits and telephone consultations will occur as necessary, as per the monitoring plan, during the course of the investigation. During the course of the study, all data will be 100% source document-verified by the monitors when possible. All subject source documents must be made available to the monitors.

13. ETHICS OF HUMAN SUBJECTS AND ADMINISTRATIVE ISSUES

13.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in the Declaration of Helsinki, EN ISO 14155:2020 Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practices, 21 CFR 803 Medical Device Reporting, International Conference of Harmonization Good Clinical Practice Guidelines and all other applicable regulatory requirements and standards. The study will also be carried out in keeping with applicable regulations and guidelines governing clinical study conduct and local legal requirements.

Each investigator confirms this by signing this study protocol.

13.2 Institutional Review Board

Before commencing with and enrolling volunteers for this proposed study, the appropriate documents (including the Protocol, Investigator's Brochure, Informed Consent Form, information sheets, CRF's and advertisements) will be submitted to the IRB. The investigator will be responsible for obtaining IRB approval for the study. Protocol deviations will also be reported to the IRB according to the policy of the board. Protocol amendments will be reviewed and approved by the IRB prior to implementation of any changes made to the study design in the amendment.

The investigators will inform the IRB:

- All subsequent protocol amendments, informed consent changes or revisions of other documents originally submitted for review
- Serious and/or unexpected adverse events occurring during the study, where required
- New information that may affect adversely the safety of the participants or the conduct of the study
- An annual update and/or request for re-approval, where required barring unforeseen circumstances, this study is anticipated to be completed within 9-10 months.
- When the study has been completed.

13.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the subjects and their families. Consent forms describing in detail the study interventions/products, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to starting intervention/administering study product. Consent forms will be IRB-approved, and the subject will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the subject and answer any questions that may arise. The subject will sign the informed consent document (ICD) prior to any procedures being done specifically for the study. The subjects should

have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The subjects may withdraw consent at any time throughout the course of the trial. A copy of the ICD will be given to the subjects for their records. The rights and welfare of the subjects 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. The subject will be asked to sign and date prior to participating in the study.

The informed consent will require a signature. Additionally, subjects will be provided with a copy of consent form to disseminate to all pertinent parties for proper discussion in order to make an informed decision concerning their participation. Should a protocol addendum be made, the subject consent form may be revised to reflect the changes of the protocol. If the consent form is revised, it is the responsibility of the investigator to ensure that an amended consent is reviewed and approved by the IRB. The approved amended consent form should be signed by all subjects subsequently entered in the study and by those subjects currently in the study, if required by the IRB. The terms of the consent and when it was obtained must also be documented in the CRF.

13.4 Participant and Data Confidentiality

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover all recorded information during the clinical study. The clinical investigation will be registered in a publicly available database. In addition, the results of the study will be published in a publicly available database.

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 monitors or other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study.

Subjects' identities will be kept confidential by assigning each subject a subject ID upon acceptance into the study. The subject ID will comprise the site ID and a three-digit number that will be based upon the subject's order of entry into the study. The study Sponsor will not receive any additional identifying information about a subject and will therefore have no way of linking a subject ID to a subject and his or her results.

13.4.1 Research Use of Stored Human Samples, Specimens or Data

ProPath may dispose of biohazard human biopsy samples per local and federal guidelines after processing of samples.

13.5 Financial Disclosure

Financial disclosures will be obtained from all investigators in order to document any potential conflicts of interest. An original Financial Disclosure Form (FDF) must be completed, signed and dated by the principal investigator (PI) and any sub-investigators. All FDFs will be collected by the Sponsor or its designee and filed in the study Trial Master File. A copy of all FDFs will be retained in the Investigator Site Binder.

13.6 Finance

The study is financed by the Sponsor. The Sponsor carries insurance that covers clinical trials, which is filed under the company's Master Policy for clinical trials conducted within the U.S.

14. DATA HANDLING AND RECORD KEEPING

14.1 Data Collection and Management

Data collection is the responsibility of the study staff at the site under the supervision of the site principal investigator. During this study the investigator must maintain complete and accurate documentation for the study.

Data management and oversight is the responsibility of the Sponsor and SGS Stephens Inc. Responsibilities include but are not limited to the following

- Clinical strategy and oversight
- Clinical study operations
- File management and study documentation
- Site initiation visit and study closeout visits
- Clinical quality assurance
- Statistical support and programming
- Data management including database development and programming and electronic data capture programming training and management

Additionally, management and oversight of photographic imaging is the responsibility of the Sponsor and SGS Stephens Inc (Clinical Research Organization).

Responsibilities may be delegated to applicable vendors.

Data will be recorded on case report forms (CRFs). A CRF is required and should be completed for each included subject.

A single-entry method will be used to enter the data captured on paper records into an electronic data capture (EDC) system. Numerical data described in Section 7 will be recorded using the SGS Stephens EDC system, which documents the identity of the evaluator/technician as well as the time and date of all entries, or all corrected entries. The

SGS Stephens EDC is a computerized system designed for the collection of clinical data in electronic format. The 3 major aspects of EDC are a graphical user interface for data entry, a validation component to check for user data, and a reporting tool for analysis of the collected data. The entries will be compared to the paper CRFs with 100% source document verification by the monitors when possible to ensure that the data is transferred accurately from the paper records to the electronic database, and any missing data and/or inconsistencies will be identified and corrected.

It is the investigator's responsibility to ensure completion, review and approve all CRFs. CRFs must be signed by the investigator or authorized staff member. These signatures serve to attest that the information contained on the CRFs are true. At all times, the investigator has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the CRFs.

Photographic images will be captured utilizing the Canfield Scientific, Inc. VISIA CA Imaging system.

14.2 Study Records Retention

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the investigator agrees to keep records including the identity of all participating subjects (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, serious adverse event forms, source documents, and detailed records of treatment disposition. The records should be retained by the investigator according to ICH guidelines of 10 years, local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another investigator, another institution, or to the Sponsor. The investigator must obtain Sponsor's written permission before disposing of any records, even if retention requirements have been met.

14.3 Protocol Deviations

A protocol deviation is any non-conformance with the conduct of the study as described in this protocol, Good Clinical Practice (GCP), or the investigational device Manual of operations.

The non-conformance may be either initiated by the subject, the investigator, or the study staff. Protocol deviations must be tracked and reported to the Sponsor in a timely manner, and corrective action implemented and documented. Protocol deviations affecting the safety of the subject or the integrity of the study must be reported by the Investigator to the IRB promptly. Reporting of all other protocol deviations must adhere to the requirements of the governing IRB.

Protocol waivers will not be allowed. However, the Investigator may implement a deviation from, or a change of, the protocol in an emergency situation to protect the rights, safety and well-being of subjects and to eliminate an immediate hazard to study subjects without prior IRB or Sponsor approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendment(s) should be submitted to the IRB for review and approval, to the Sponsor for agreement, and to the regulatory authorities, if required.

14.4 Publications and Data Sharing

The publication policy will be in accordance with the investigator agreement with each principal investigator or similar agreement. No information on individual subjects will be revealed in any publications or presentations.

The SGS Stephens group will compose the study report for the Company Sponsor.

15. LITERATURE REFERENCES

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Appendix Section

Appendix A: Glogau Photodamage Scale

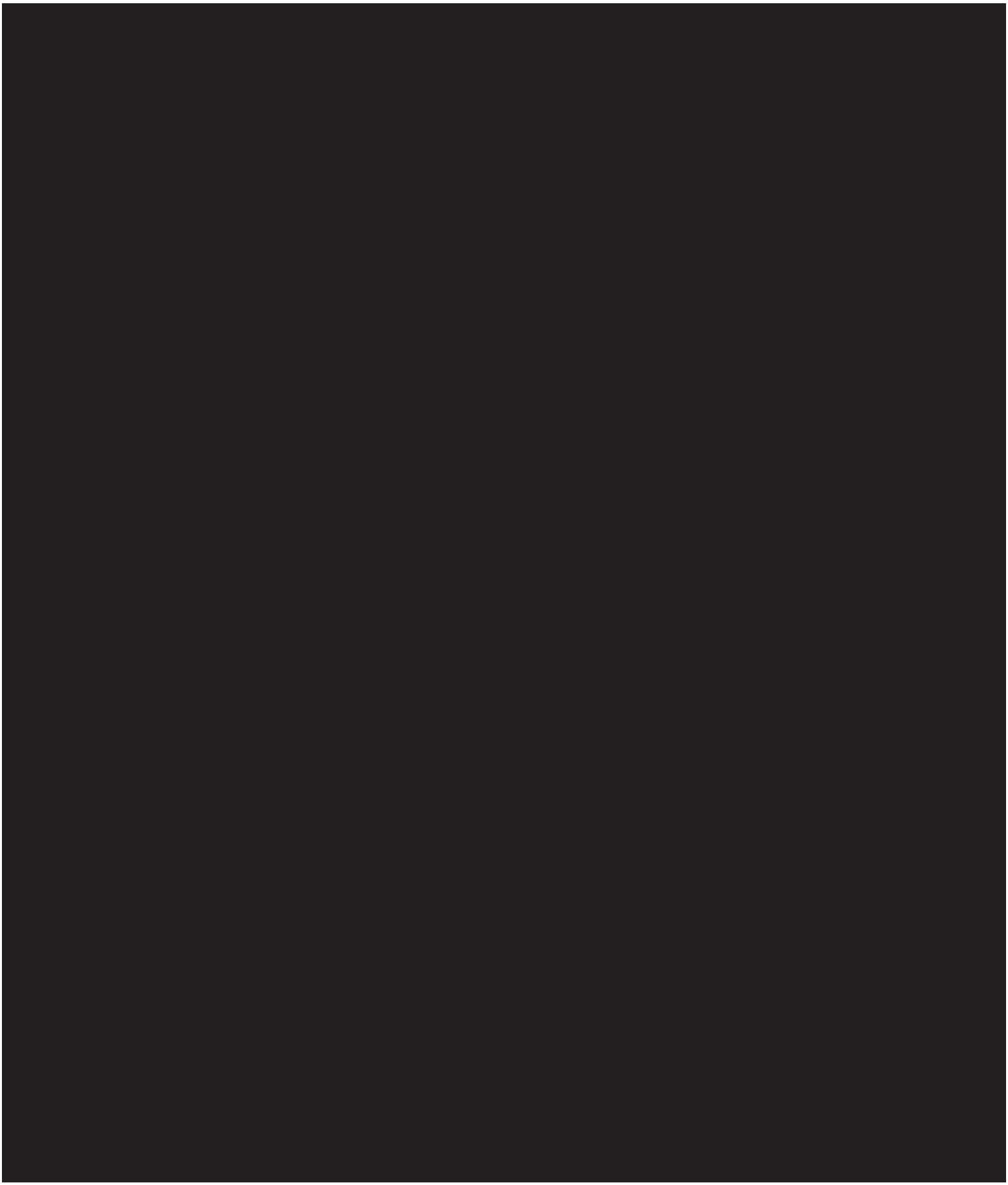
Glogau Photodamage Scale			
Group Classification	**Typical Age**	**Description**	**Skin Characteristics**
I Mild	28-35	No Wrinkles	Early Photoaging: mild pigment changes, no keratosis, minimal wrinkles, minimal or no makeup
II Moderate	35-50	Wrinkles in motion	Early to Moderate Photoaging: Early brown spots visible, keratosis palpable but not visible, parallel smile lines begin to appear, wears some foundation
III Advanced	50-65	Wrinkes at rest	Advanced Photoaging: Obvious discolorations, visible capillaries (telangiectasias), visible keratosis, wears heavier foundation always
IV Severe	60-75	Only wrinkles	Severe Photoaging; Yellow-gray skin color, prior skin malignancies, wrinkles throughout-no normal skin, cannot wear makeup because it cakes and cracks

Appendix B: Fitzpatrick Wrinkle and Elastosis Scale

Fitzpatrick Wrinkle and Elastosis Scale			
Class	**Wrinkling**	**Score**	**Degree of Elastosis**
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 popular 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.

Appendix C: Fitzpatrick Skin Type

Fitzpatrick Skin Type			
Skin Type	**Usual Characteristics**	**Descent/Ethnicity**	**Burn/Tan**
I	White; very fair; red or blond hair; blue eyes, often freckles.	Redheads, Celtics, Irish, Scottish	Always burns, never tans
II	White; fair; red or blonde hair; blue, hazel or green eyes, often freckles.	Caucasians	Usually burns, tans with difficulty
III	Cream white; fair with any eye or hair color	Caucasians	Sometimes mild burn, gradually tans
IV	Brown; typical Mediterranean, Caucasian skin	Mediterranean, Asians, Hispanics, American Indian	Rarely burns, tans with ease
V	Dark browns; Middle Eastern skin types	Middle Eastern, East Indian, some Hispanics, some African Americans, some Asians	Very rarely burns, tans very easily
VI	Black	Usually African	Never burns, tans very easily



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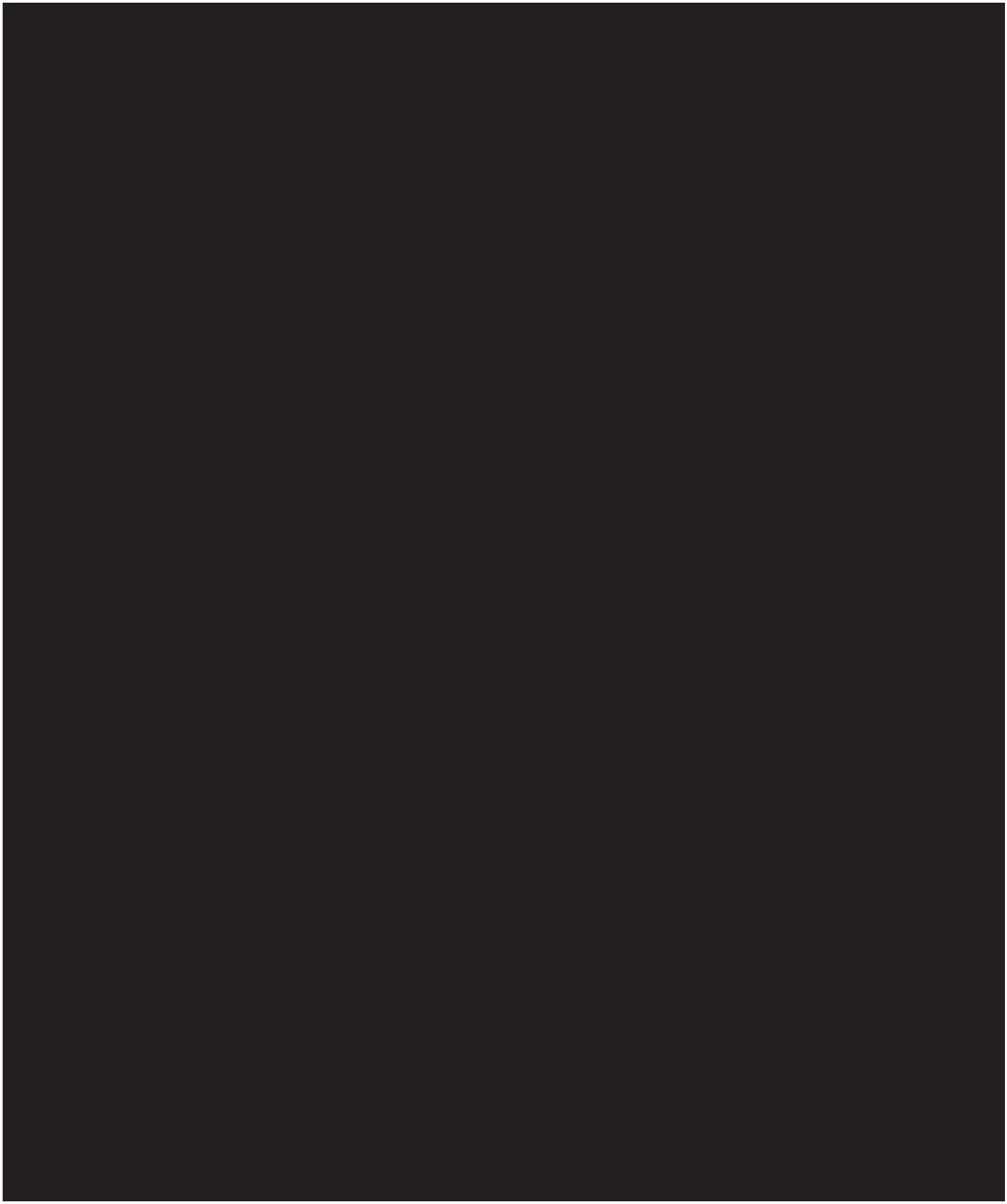

Appendix F: Patient Skin Response Seven-Day Diary

Using the severity scale, please rate the following conditions after your treatment:
Answer for all conditions each day:

	0= None 1= Mild 2= Moderate 3= Severe	Rating
Day 1	Erythema (redness)	
	Edema (swelling)	
	Heat sensation after treatment	
Day 2	Erythema (redness)	
	Edema (swelling)	
	Heat sensation after treatment	
Day 3	Erythema (redness)	
	Edema (swelling)	
	Heat sensation after treatment	
Day 4	Erythema (redness)	
	Edema (swelling)	
	Heat sensation after treatment	
Day 5	Erythema (redness)	
	Edema (swelling)	
	Heat sensation after treatment	
Day 5	Erythema (redness)	
	Edema (swelling)	
	Heat sensation after treatment	
Day 6	Erythema (redness)	
	Edema (swelling)	
	Heat sensation after treatment	
Day 7	Erythema (redness)	
	Edema (swelling)	
	Heat sensation after treatment	