ERCHONIA® CORPORATION GVS

An Evaluation of the Erchonia Corporation GVS Laser As a Non-Invasive Treatment to Improve the Appearance of Skin Laxity on the Abdominal Region

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STUDY INFORMATION

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PURPOSE OF STUDY
The purpose of this clinical study is to determine the effectiveness of the Erchonia® GVS, manufactured by Erchonia Corporation (the Company), in improving the appearance of skin laxity on the abdominal region.

STUDY DURATION
The estimated total duration of the study is 16 weeks.

INDICATION FOR USE
The indication (claim) being sought through support of the results of this clinical study is:

"The Erchonia GVS is indicated for use as a non-invasive dermatological aesthetic treatment to improve the appearance of skin laxity on the abdominal region".

The indication for use being sought for the Erchonia GVS through the outcome of this clinical study is comparable to those attained under the following 510(k)s:

- **K233104:** The SofWave System is indicated to improve the appearance of skin laxity on the upper arms

- **K211483:** The SofWave System is indicated for use as a non-invasive dermatological aesthetic treatment to improve … the appearance of lax tissue in the submental and neck regions

- **K223856:** The NuEra Tight RF and NuEra Tight RF Plus are intended to provide … abdominal circumference reduction with adjunctive improvement in the appearance of skin laxity

It is intended that the results of this clinical study be used to support a 510(k) submission to attain FDA market clearance for the Erchonia GVS for the intended indication for use.

EXPECTED RESULTS
Twelve weeks post-final treatment, it is anticipated that compared with pre-treatment, at least 80% of subjects will demonstrate an improvement in the appearance of skin laxity on the abdominal region, defined as at least 2 of the 3 blinded evaluators correctly identifying the post-treatment photograph for 80% of subjects.

The study success criteria and 12-week post-final treatment primary endpoint evaluation is identical to the FDA market clearances obtained by SofWave Systems (K233104 and K211483)

REGULATORY BACKGROUND
The Erchonia GVS Laser emits non-thermal and non-invasive green and violet low-level laser light, the technology of which has an extensive regulatory background and has obtained multiple FDA clearances under the following product codes:

- OLI for non-invasive fat loss
- NHN for adjunctive use in pain therapy
- PDZ for temporary increase of clear nail in patients with onychomycosis
- GEX for general and plastic surgery and in dermatology

Each of the below market clearances pertain to Erchonia laser devices utilizing either Erchonia green or violet laser technology. Each was supported by efficacy data from a pivotal full-scale controlled and powered clinical trial.

- **K142042:** The Erchonia® SHL Laser is indicated for use as a non-invasive dermatological aesthetic treatment for reduction of circumference of hips, waist and upper abdomen when applied to individuals with a Body Mass Index (BMI) between 30 kg/m² and 40 kg/m².
- **K123237:** The Erchonia® Zerona™ 2.0 Laser is indicated for use as a non-invasive dermatological aesthetic treatment as an adjunct for individuals intending to undergo liposuction procedures for the reduction of circumference of hips, waist, and thighs.
- **K231474:** The Erchonia® Violet ZERONA Z6 OTC is indicated for use as a non-invasive dermatological aesthetic treatment for the reduction of body circumference.
- **K130922:** The Erchonia® Verju Laser System with Massager is indicated for use as a non-invasive dermatological aesthetic treatment as an adjunct for individuals intending to undergo liposuction procedures for the reduction of circumference of hips, waist, and thighs. The Massager component is indicated for the temporary reduction in the appearance of cellulite.
- **K191257:** The Erchonia® EVRL laser is generally indicated:
  a. while using the red and violet diode simultaneously, for adjunctive use in providing

temporary relief of minor chronic neck and shoulder pain of musculoskeletal origin
b. and while using the violet diode, to treat dermatological conditions, and specifically indicated to treat moderate inflammatory Acne Vulgaris

- **K221987:** The Erchonia® GVL laser is generally indicated:
  a. while using the green and violet diode simultaneously, for adjunctive use in providing temporary relief of minor chronic neck and shoulder pain of musculoskeletal origin
  b. and while using the violet diode, to treat dermatological conditions, and specifically indicated to treat moderate inflammatory Acne Vulgaris.
- **K153164:** The LunulaLaser™ device is indicated for use for the temporary increase of clear nail in patients with onychomycosis (e.g., dermatophytes Trichophyton rubrum and T. mentagrophytes, and/or yeasts Candida albicans, etc.)

REGULATORY PATHWAY
The results of this clinical study are intended to support a 510(k) submission to the FDA under product code GEX:

Photobiomodulation (PBM) devices, also known as low-level light therapy (LLLT) devices, utilize light at an irradiance level that does not generate heat, with the goal of modifying biological activity. The FDA recognizes this mechanism, as noted in its recently issued Draft Guidance for Industry on Photobiomodulation Devices (PBMs). In this guidance, the GEX code is identified as a relevant product classification.

† *Photobiomodulation (PBM) Devices - Premarket Notification [510(k)] Submissions, Draft Guidance for Industry and Food and Drug Administration Staff. January 12, 2023.*

The Erchonia EVRL, which emits an identical violet laser as the Erchonia GVS, has been cleared under the GEX code for the treatment of dermatological conditions, including its specific indication for moderate inflammatory Acne Vulgaris (K152196). Other LLLT devices have also received clearance under the GEX product code for dermatological applications, such as the treatment of superficial benign vascular and pigmented lesions (K160880, K210535, K202361).

Based on these precedents, the results of this clinical trial are intended to support submission under the GEX product code for clearance of the Erchonia GVS as a non-invasive dermatological aesthetic treatment to improve the appearance of skin laxity on the abdominal region".

STUDY DEVICE: THE ERCHONIA® GVS

DEVICE DESCRIPTION
The Erchonia® GVS Laser is designed for clients seeking noninvasive improvement in appearance of abdomen skin laxity without invasive surgery. The GVS Laser allows the patient to continue their daily activities without interruptions from surgery, pain, wounds or garments. The GVS utilizes photochemical reactions to enhance collagen production and improve blood circulation, leading to firmer skin.

The GVS Laser was built on the clinical foundation of its predecessors, the Erchonia Emerald, Verju, and Violet Zerona which were proven through clinical studies to be safe and effective in the application of noninvasive fat loss. The Erchonia® GVS Laser used in this study is a robotic scanner low-level laser that uses twelve semi-conductor diodes, including (6) 520 nanometer

diodes and a (6) 405 nanometer diodes, each emitting its wavelength with a tolerance of ±10 nanometer. The laser diodes are classified as a Class II Laser in accordance to IEC 60825-1 (complies with 21 CFR 1040.10 and 21 CFR 1040.11 by Laser Notice #50).

The twelve laser diodes utilize internal mechanics that collect the light emitted from the laser diode and rotate the light in a spiraling circle pattern that is totally random and independent of the other diodes. The laser head assembly can be manually adjusted for positioning the lasers 3-4 inches from the patient's skin to deliver treatment for skin laxity. The device laser head assembly can be moved vertically (raised or lowered) over the subject for proper placement of lasers for treatment. The device laser head assembly can be moved horizontally (left or right) over the subject for proper placement of lasers for treatment.

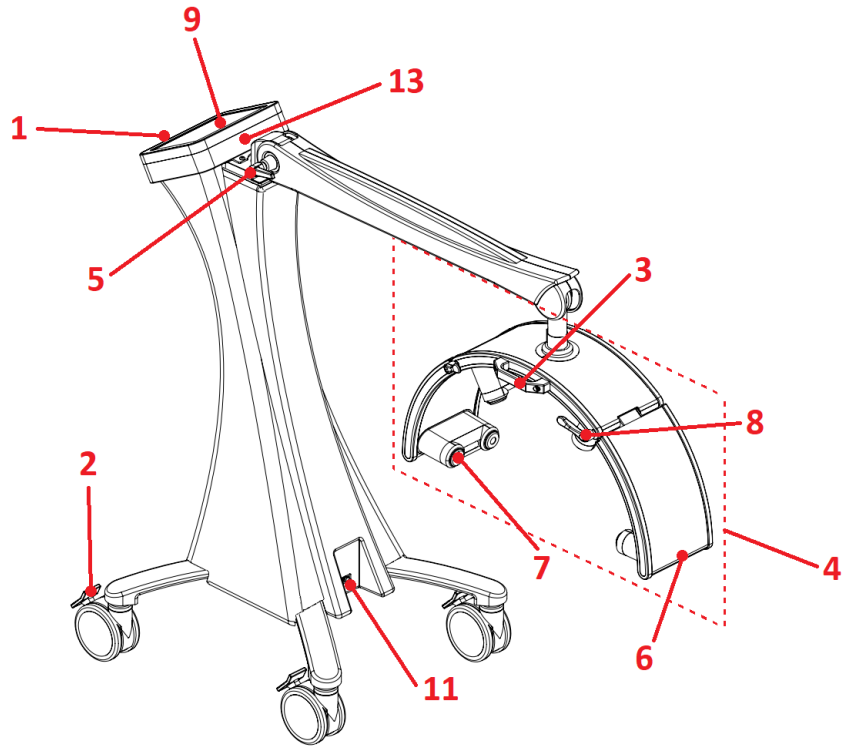
The device contains software that is loaded into PCB drivers. This data includes the touch screen images (GUI) and the command prompts that activate the screen icons; work in conjunction with the component platform to ensure the device operates as intended.

Physical Characteristics
The Erchonia® GVS is made of PT8952 Polyurethane (Enclosure), 6061-T6 AL, 6063 AL, 5052 AL (Legs, Handles, Arms, Support Structure, Touchscreen Enclosure), Kydex T (Covers), and all other components are Acetal.

The associated accessories include:

Device Accessories:

- Laser safety glasses
- Tape measure
- Manual
- External Power Supply
- Power cord



1. Device Handle
2. Wheel Lock
3. Head Handle
4. Laser Head
5. Spring Arm Lock
6. Laser Arms
7. Laser Output Heads
8. Laser Arm Locks
9. Touchscreen
10. External Power Supply
11. Power Inlet
12. Power Cord
13. Power Pushbutton

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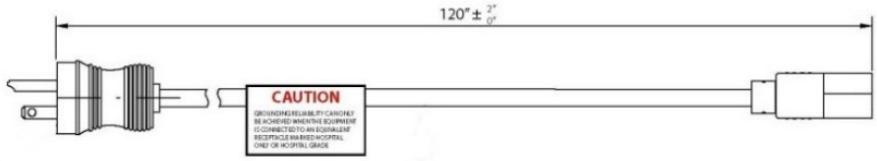

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DEVICE SPECIFICATIONS

- Weight: 90lbs / 41kg
- Height: 68in / 173cm (Average – Adjustable)
- Full Color Touch Screen Control Center
- Two independent adjustable Laser Arms
- 4 locking Anti-static casters
- Powder coated touchscreen enclosure
- Non-allergenic material finished with paint
- Applied Part: Type B
- Leakage Current 0.3 -0.5 µA (Micro Amps)

Laser

- Twelve line generating diode modules
  (6) Violet laser diodes
  (6) Green Laser diodes
- Output:
  Violet: 23.00mW +/- 2.00mW
  Green: 16.00mW +/- 2.00mW
- Wavelength:
  Violet: 405nm +/- 10nm
  Green: 520nm +/- 10nm
- Duty Cycle: CW (Continuous 100%)

Power

- Source: 100-240VAC 50-60Hz

Temperature

- Operating Temp: 59 to 85°F (15 to 29°C) <50% Relative Humidity
- Transporting: -22 to 158°F (-30 to 70°C) <75% Relative Humidity

Device Handle [1]
The Device Handle gives the operator the ability to move the device for proper positioning to client for accurate treatment location as well as move the device for storage or relocate to a different room.

Wheel Lock [2]
The device includes four antistatic wheels that enable ease for maneuverability. Once the device is transported to the desired location, the wheel locks can be engaged to eliminate excessive movement of the device.

Head Handle [3]
The Head Handle gives the operator the ability to raise or lower the Laser Head [4] for proper positioning to the client.

Laser Head [4]
The Laser Head located on the end of the main arm accommodates the Laser Arms [6], the eight Laser Output Heads [7], the Laser Arm Locks [8] and the Head Handle [3]. This assembly can be raised or lowered by means of the Head Handle [3].

Spring Arm Lock [5]
The Spring Arm Lock is the black lever attached to the side of the main arm. The arm tension can be adjusted or locked into position with the Spring Arm Lock for proper positioning to the client.

Laser Arms [6]
There are two Laser Arms on the device, each arm houses two Laser Output Heads [7]. The Laser Arms are designed to be adjusted by intentional force from the operator, allowing the operator to angle the Laser Output Heads in and out for proper positioning to client.

Laser Output Heads [7]
There are twelve Laser Output Heads on the device. These heads are housed in plastic and accommodate the lens, laser diodes, motors, and their associated electronics.

Laser Arm Locks [8]
The Laser Arm Locks are black levers attached to the side of the Laser Arms [6]. To angle the Laser Arms in or out, the Laser Arm Locks are loosened by turning the lever lock counterclockwise. Once the Laser Arm are moved to the proper treatment distance and position the Laser Arm Locks are tightened by turning the lever lock clockwise.

Touchscreen [9]
The Touchscreen functions as a display screen and an input panel, providing information to the user and a means to operate the device by touching the appropriate icon.

External Power Supply [10]
The External Power Supply is an AC/DC converter that is required to power the device. The power supply must be plugged into the device Power Inlet (11) and the Power Cord (12), with the other end of the power cord plugged into a wall socket, to power the device.

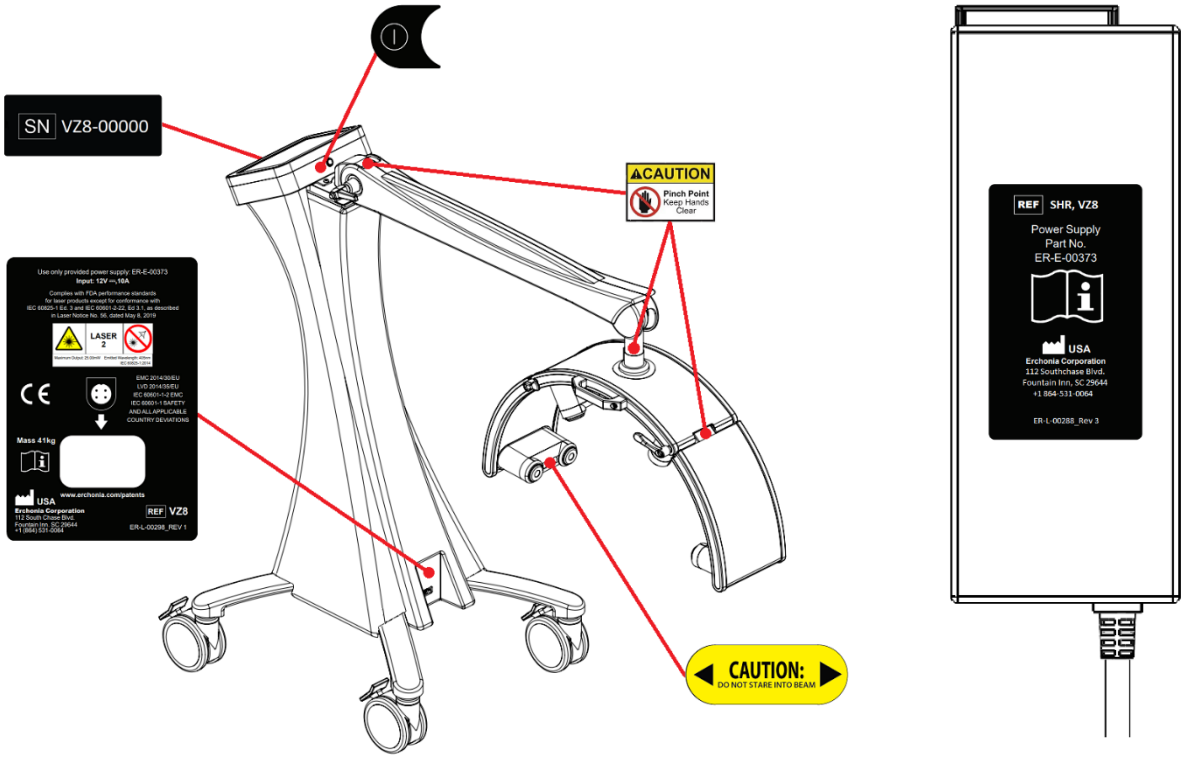
Power Inlet [11]
The device contains an appliance coupler (Power Inlet) and a flexible detachable Power Cord [12]. This is the location on the device where the External Power Supply [10] is connected.

Power Cord [12]
The device contains a hospital grade flexible detachable Power Cord. The Power Cord plugs into the External Power Supply [10] prior to plugging the other end into a wall socket.

LABELING

The Erchonia® GVS to be used in this clinical study will be labeled, **"CAUTION – Investigational device**. Limited by United States law to investigational use." Once the device has been cleared for market in the U.S., the device will be labeled as a prescription device, per 21 CFR § 801.109.

The following diagram shows the location of the compliance label, power pushbutton label, serial number label, three identified pinch point labels, and one of the (6) laser labels, indicating the direction of the laser beam output with caution-do not stare into beam. Integrated into the compliance label is the electrical input detail containing Volts and Amps specifications. The large black background label is this primary label and is compliant to FDA and ISO standards; the image captures the FDA code regulated classifications and International criteria. As a class 2 laser equipment the compliance label includes the class 2 laser caution label notifying not to stare into the laser beam.



SAFETY

Protective Eyewear

The Erchonia® GVS is classified by the IEC as a Class 2 laser device. This designation represents a current standard for use in order to ensure the safety of the patient. A Class 2 laser is determined to have a chronic viewing hazard. Pointing the laser beam directly into the eye and maintaining it there for an extended period of time could prove to be damaging. To ensure there is no possible instance of residual effect, we have included a pair of specialty glasses for use by the patient during treatment. 100-10-110 is an ultra-light-weight comfortable frame with a double coated scratch-resistant polycarbonate laser filter. The fit-over-prescription style frame offers universal fit with wide field of view. Lens has superior optical clarity with virtually no distortion to reduce eye fatigue. It is ideal for use in most laser applications and comfortable for long periods of wear. These safety glasses sufficiently and effectively block the laser light spectrum at OD 6+ @ 190-532 nm, OD 6+ @ 10,000-11,000 nm.

Height: 63.8 mm
Width: 155.3 mm
Length: 140-160 mm

⚠	WARNING- The patient should always be correctly fitted with the safety glasses provided before turning on the laser and doing any treatment.

STUDY BACKGROUND AND RATIONALE

STUDY INDICATION: ABDOMINAL SKIN LAXITY

Definition of Abdominal Skin Laxity

Skin laxity is defined as the acquired loose, relaxed state of the skin that develops from skin extensibility (stretch) and decreased skin recoil (return to original state after stretch). Skin laxity of the abdomen is visible as the appearance of loose and sagging skin on the stomach that results from a loss of elasticity.

Causes of Abdominal Skin Laxity

Intrinsic and extrinsic aging causes specific cutaneous changes, such as epidermal thinning, loss of collagen, degradation of elastin, and redistribution of subcutaneous fat, that all lead to significant abdominal skin laxity. However, there are several additional factors that can exacerbate the appearance and accelerate the onset of abdominal skin laxity include advanced age, key amongst which are the following:

- *Weight Loss:* Significant, especially rapid, weight loss, can leave skin stretched and unable to contract back to its original shape, resulting in loose skin.
- *Pregnancy:* Pregnancy stretches the skin of the abdomen, and postpartum, the skin may not fully return to its original state, leading to sagging.
- *Genetics:* Some individuals may be genetically predisposed to developing skin laxity, without additional contributing factors.
- *Sun Exposure:* Prolonged sun exposure can damage collagen and elastin, leading to sagging, and premature aging.
- *Smoking:* Smoking leads to a reduction in collagen production and damage to existing collagen, resulting in loose, sagging skin

Currently Available Treatments

Current treatment options for abdominal skin laxity include both surgical and non-surgical modalities; invasive, minimally invasive, and non-invasive.

Surgical treatment options include:

- *Abdominoplasty (Tummy Tuck):* Surgical removal of excess skin and fat from the abdomen and tightening of the underlying abdominal muscles.
- *Mini Tummy Tuck:* A smaller version of a traditional tummy tuck, addressing less severe skin laxity and fat.
- *Liposuction:* Removal of stubborn fat deposits to improve the appearance of loose skin through suctioning out of fat through inserted cannulas.
- *Excess Skin Removal Procedures:* Surgical removal of excess skin after significant weight loss.

Non-surgical treatment options include:

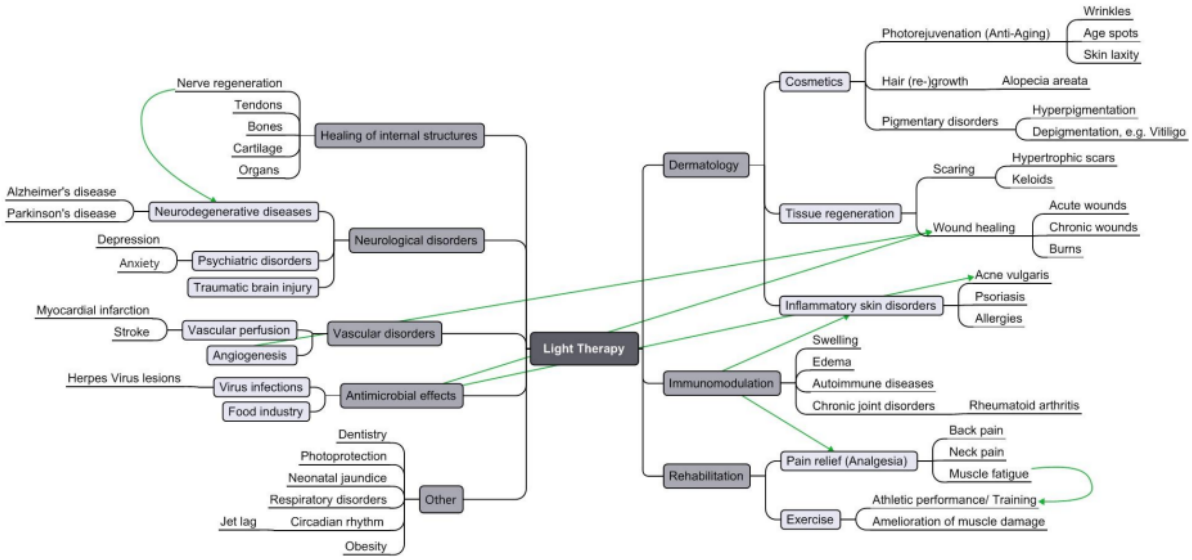
- *Radiofrequency (RF) Treatments:* Radiofrequency energy is used to heat the deeper layers of the skin, stimulating collagen production and improving skin tightness. RF devices commonly used for this application include BodyTite, and Morpheus8
- *Ultrasound Therapies:* Ultrasound energy is applied to heat the skin, similarly to RF, to promote collagen production and skin tightening. Examples include HIFU (High-Intensity Focused Ultrasound)
- *Laser Skin Tightening:* Laser application stimulates collagen production and improves skin elasticity. Examples include Fractional laser therapy, CO2, and erbium lasers

- *CoolSculpting:* This procedure uses cryolipolysis (fat freezing) to reduce fat cells in the abdomen, which can improve the appearance of loose skin.
- *Profhilo:* An injectable treatment that improves skin laxity and hydration.
- *Topical Treatments:* Creams and lotions to help improve skin elasticity and hydration,
- *Lifestyle Changes:* A healthy diet, regular exercise, and staying hydrated can help improve skin tone and elasticity.

THEORY OF MECHANISM OF OPERATION OF THE APPLICATION OF ERCHONIA® LASERS FOR IMPROVING THE APPEARANCE OF SKIN LAXITY

Following from the above cumulative research, and observations noted from clinicians across the administration of numerous treatments, it is a logical inference that application of Erchonia low level laser therapy will also affect an improvement in skin laxity to the target area of the abdomen.

From a biological perspective, low-level laser therapy (LLLT) application initiates a photochemical reaction in cells that alters their biological activity. The primary target of this light therapy is the mitochondria, the cell's energy-producing organelles. Specific wavelengths of light are absorbed by protein complexes within the mitochondrial electron transport chain. This translates to enhanced oxidative phosphorylation, the main cellular process for generating adenosine triphosphate (ATP), the fundamental energy molecule powering cellular functions. LLLT influences a broad spectrum of biological activity, with research suggesting a regulation of over 100 genes, impacting various cellular processes like growth, collagen synthesis, microcirculation, apoptosis (programmed cell death), DNA repair, and antioxidant activity [3].



Collagen is a fundamental structural protein essential for maintaining skin firmness, elasticity, and resilience. When collagen production declines due to external factors, age, or significant weight loss, the skin loses its strength and support, leading to increased laxity, sagging, and reduced elasticity. This weakening of the skin's structure is a primary concern in aesthetic

treatments focused on improving skin tightness and tone. Green low-level laser therapy (LLLT), such as that emitted by the Erchonia GVS, may help stimulate collagen synthesis and enhance dermal structure. A study published in the *Journal of Cosmetic Dermatology* confirmed that low-level green laser therapy enhances the secretion of Collagen I and III, contributing to improved skin structure and firmness [4].

Research by Seo et al. (2014) found that green light upregulates the expression of collagen type I and TGF-β1, a key growth factor that regulates collagen production and tissue remodeling [5]. TGF-β1 binds to fibroblast receptors, activating SMAD proteins that trigger the genes responsible for collagen synthesis (COL1A1 and COL3A1), ultimately strengthening and tightening the skin. Green light has also been found to induce leptin [6], a signaling molecule that stimulates fibroblast proliferation, boosts collagen production, and supports angiogenesis, improving blood flow and nutrient delivery to the skin. Moreover, green light has demonstrated a significant ability to stimulate fibroblast proliferation compared to red and infrared wavelengths [7], further supporting its potential role in skin tightening.

Nitric oxide (NO) is another crucial factor in maintaining skin firmness and elasticity, playing a key role in reducing skin laxity. As a vasodilator, NO increases blood flow, ensuring that oxygen and essential nutrients reach skin cells to sustain collagen synthesis and maintain skin tightness. Additionally, NO has antioxidant and anti-inflammatory properties that help prevent collagen degradation, which can contribute to skin laxity, particularly following rapid fat loss.

Research has shown that exposure to violet/blue light, similar to that of the Erchonia GVS, can significantly increase NO production in the skin, triggering biological responses that improve circulation and oxygenation (8). Blue laser irradiation has been found to enhance local tissue perfusion by stimulating the controlled release of NO from nitrosyl-hemoglobin (NO-Hb) complexes (9). These mechanisms suggest that blue laser therapy may help support skin elasticity and firmness by promoting NO release, potentially aiding in the prevention of skin laxity after significant weight loss.

Modulating inflammation, particularly by reducing IL-6 and IL-8, can enhance fibroblast function, leading to improved collagen synthesis and tissue repair. Fibroblasts play a crucial role in wound healing by producing extracellular matrix components, including collagen, which provides structural integrity to healing tissues. Similarly, IL-8 is a pro-inflammatory cytokine that attracts neutrophils to injury sites, contributing to prolonged inflammation. Persistent IL-8 expression can delay the transition from inflammation to the proliferative phase of wound healing, affecting fibroblast activity and collagen deposition. Violet laser therapy has demonstrated effectiveness in reducing inflammatory cytokines, such as interleukin-6 (IL-6) and interleukin-8 (IL-8) [10]

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RATIONALE AND JUSTIFICATION FOR CURRENT STUDY AND INDICATION

According to the American Society of Plastic Surgeons (ASPS) 2023 Procedural Statistics Release:

- Whether through surgical toning or noninvasive treatments, patient focus was on the pursuit of a holistic, well-rounded approach to body enhancement that catered to both the challenges of weight loss and the natural effects of aging.
- The 2023 data show a significant interest in body-centric procedures performed, increasing 7% overall from 2022, with a particular focus on procedures to refine, contour, and tighten lax skin.
- Abdominoplasties (tummy tucks) evidenced a 5% increase in 2023 over 2022 with 170,110 procedures performed.
- Liposuction remained the number one performed procedure in 2023, increasing 7% from 2022.
- Minimally invasive treatments grew 7% in 2023 relative to 2022, equally for men and women, driven by advancements in technology and patient preference for less cost, less downtime, and almost immediate results.
- Non-invasive skin tightening procedures such as Pelleve®, Thermage®, and Ulthera® grew by 7%, and non-invasive fat reduction procedures such as CoolSculpting®, Liposonix®, Emsculpt®, Vanquish®, Zerona®, and Kybella® grew 9%.

Low-level light therapy (LLLT) is a fast-growing technology, proven and FDA market cleared for non-invasive body contouring, including the area of the abdomen. It has also been proven effective in improving skin laxity. As explained in detail above, the skin responds well to LLLT wavelengths where the laser photons are absorbed by mitochondrial chromophores in cells leading to an increase in adenosine triphosphate (ATP) release thus improving blood flow and reactive oxygen species.

It therefore follows that the Erchonia GVS is ideally suited to effecting a statistically significant and clinically meaningful aesthetic improvement in the appearance of skin laxity of the abdomen of males and females following completion of administration of the full treatment protocol, thus providing a viable and desirable option for the ever-growing patient population seeking cost-effective non-invasive treatment alternatives with minimal to no downtime for improvement in the appearance of abdominal skin laxity.

STUDY DESIGN AND METHODOLOGY

STUDY DESIGN
This clinical study is a prospective single-arm design with post-hoc analysis of study primary efficacy by independent blinded evaluators intended to evaluate the efficacy of the Erchonia® GVS Laser in providing noninvasive improvement in the appearance of skin laxity of the abdomen region.

SUBJECT GROUP
There is a single active treatment only subject group in this study.

RANDOMIZATION
As all enrolled subjects in this study will knowingly receive the active study treatment with the Erchonia® GVS, randomization to treatment group is not applicable.

STUDY BLINDING
As all enrolled subjects in this study will knowingly receive the active procedure administration with the Erchonia® GVS, neither the subjects nor the study investigators will be blinded.

However, key study outcome assessments, including primary study success determination, will be blinded through use of three (3) Independent Blinded Evaluators who will assess study outcomes through evaluation of coded, deidentified photographs provided in randomized order post-study endpoint. The digital photographs will be presented to each Independent Blinded Evaluator in blinded coded randomized fashion that will be different for each Evaluator. Randomization of photograph presentation order will additionally occur across test sites. Each Independent Blinded Evaluator will perform and record the pre-determined outcome assessments independently of each other, without input, consultation, comparison of determinations, or any other form of interaction or communication with each other during the assessment process. The Independent Blinded Evaluators will not have otherwise been involved with any aspect of study design or execution.

Randomization of order of subject post-hoc photo presentation within and between Independent Blinded Evaluators, as applicable to the outcome assessment being performed, will be attained using computer generation sequence methodology (www.randomization.com) ensuring that the randomization methodology and the generated allocation sequence is concealed from the Independent Blinded Evaluators. Each computer-generated randomization sequence is unique and will therefore not be able to be replicated.

Additional clinically important measures are objective.

INDEPENDENT BLINDED EVALUATORS
Independent Blinded Evaluators participating in this study will be licensed and qualified physicians such as MD's, DO's, Dermatologists, Plastic surgeons, Cosmetic surgeons, and Board-certified weight loss physicians who are trained and experienced in visualizing, treating, and observing for change in skin laxity.

SUBJECTS
Subject Sample
Subjects will be males and females 22 years or older who present with visible skin laxity (loose skin) in the abdomen region and who subsequently satisfy all qualification criteria.
Sample Size

There will be 35 qualified subjects enrolled in this study.

Rationale for Sample Size

In consideration of the primary assessment, a clinically important outcome is pre-established as at least 2 of the 3 blinded evaluators correctly identifying a subject's pre-treatment and post-treatment (study endpoint) photographs, with study success occurring when this is attained for 80% or more of subjects.

Consequently, the planned sample size to provide sufficient power for a statistical comparison of the proportion of treatment responders (P) versus a reasonable cutoff (P0) is based on a power calculation utilizing the (one proportion) binomial exact test based on the following assumptions.

- H0: $P \leq P0$ versus Ha: $P > P0$
- Type I error rate: $\alpha = 0.025$
- Power = 90%
- Population proportion under the null hypothesis: P0 = 0.80
- Population proportion under the alternative hypothesis: P = 0.50
- Total N = 30 study participants

To account for a possible 15% subject attrition rate, a total of 35 subjects will be enrolled.

Recruitment

Subjects will be recruited from among:

(i) The test site's pool of existing and new clients
(ii) Subjects who respond to the recruitment materials found in **Appendix C.**

Compensation

A subject who completes his or her participation in this clinical study through to the final post-treatment administration visit will receive financial compensation of $100.

A subject will not be charged for the cost of the use of the device or administration of the study treatments with the Erchonia® GVS Laser or for the cost of any other directly related evaluations or measurements that occur as part of his or her participation in the study.

STUDY PROCEDURE

STUDY TEST BATTERY

The following is a listing of the study assessment tools to be used and the variables to be recorded in this study. For each study phase, the precise tools from this list that will be employed will be specified.

STUDY QUALIFICATION EVALUATION

Skin Laxity Scale

The Skin Laxity Scale, commonly used both clinically and in published research to assess the degree of skin laxity, is a simple assessment scale that can be applied to determine degree of skin laxity in any body area according to the following 0-3 scale from either live assessment or through post-hoc assessment of images:

- 0 = no laxity
- 1 = mild
- 2 = moderate
- 3 = severe

BASELINE VARIABLES

Subject Demographics

- Gender: male or female
- Age (years)
- Ethnicity: Hispanic or Latino. Not Hispanic or Latino
- Race: Caucasian/White, Hispanic/Latino, African American/Black, American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, Other

Medications and Procedures

- Current medications (OTC, prescription) taken for/with weight loss indications: dose, frequency of use, duration of use
- Prior medications (OTC, prescription) taken for/with weight loss indications: dose, frequency of use, duration of use
- Procedures undertaken for weight loss indications: duration since performed
- Concomitant medications (OTC, prescription) routinely taken by the subject for indications other than weight loss: indication, dose, frequency, duration of use

Diet and Exercise

- Details of the subject's typical daily diet (food and drink consumption), including type of diet followed if applicable (e.g. Keto, Vegetarian, Vegan, Pescetarian, high protein, Atkins, Weight Watchers, etc.)
- Typical exercise patterns type (e.g. running, gym, dance classes, walking, etc.) and frequency.

OUTCOME ASSESSMENT TOOLS

OBJECTIVE ASSESSMENTS

- **Body Weight:** recorded in kilograms (kg)
- **Height:** recorded in inches (in)

- **Body Mass Index (BMI):** calculated as the ratio of weight in kilograms to height in meters squared (m^2).
- **Waist and Hips Circumference:** Circumference in inches (ins) for the subject's waist and hips will be measured according to the following protocol at all assessments to ensure consistency across the study:

  - ✓ Hip circumference: measurement will be made such that both hip bones are encircled
  - ✓ Waist circumference: distance in inches from the hip bone to the point at which the circumference of the waist is measured (at the subject's natural waist formation) will be recorded after first measurement to allow for consistent post-treatment measurements

  Potential inter-investigator variability will be removed through standardization and training of a sole assessor at each test site.

PRIMARY OUTCOME MEASURE

DIGITAL PHOTOGRAPHS: Subjects will be photographed in a standing position, with relaxed posture. High-resolution digital images will be taken of the subject's abdominal area from the frontal view, and each of the right and left views, at each evaluation visit. Photographs will be acquired using a standardized photography set-up (Google Pixel 8 Pro [50-megapixel], ring light tripod) to ensure consistency, and will be taken in a standardized manner in the same room under the same lighting conditions, with effort made for the images to be taken by the same individual, with the same system settings fixed at the same location, with all subjects situated at the same distance from the lens for each photograph. At each post-baseline visit, the photographer will refer to the baseline photographs to ensure consistency in subject positioning and exposure. Additionally, subjects will be required to wear the same clothing to the test site each time photographic imaging will occur. The same photo imaging control protocols will be employed across all study test sites.

Detailed instructions for the photographs are contained in **Appendix B: Photograph Methodology Instruction Sheet.**

GLOBAL AESTHETIC IMPROVEMENT SCALE: SUBJECT AND PRINCIPAL INVESTIGATOR

The **Global Aesthetic Improvement Scale (GAIS)** is a widely used subjective qualitative assessment tool in clinical trials to evaluate the effectiveness of aesthetic interventions from before to after treatment using a five-point scale ranging from "3: very much improved" to "-1: worse," that enables investigators to provide a standardized evaluation of treatment outcomes. GAIS has demonstrated reliability and clinical relevance and has been validated in multiple studies for use by both the investigator and the subject to assess improvement following aesthetic interventions, including skin laxity.

The Global Aesthetic Improvement Scale Assessment (GAIS) is as follows:

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

SUBJECT SATISFACTION WITH STUDY OUTCOME: The subject is asked to rate how satisfied he or she is with any change in the appearance of the skin laxity of the abdomen region following completion of the laser administration procedure with the Erchonia® GVS by using the 5-point Likert scale below to respond to the following question: “Overall, how satisfied or dissatisfied are you with any change in the appearance of the skin of your abdomen following the study procedures with the study laser device?”

- Very Satisfied
- Somewhat Satisfied
- Neither Satisfied nor Dissatisfied
- Not Very Satisfied
- Not at All Satisfied

SUBJECT-REPORTED PERCEPTION OF SKIN TIGHTNESS: Following the completion of the laser treatment with the Erchonia® GVS device, subjects will be asked to assess perceived changes in abdominal skin tightness. Using the 5-point Likert scale provided below, subjects will respond to the question: “Overall, compared to before your treatment with the study device, how much tighter does the skin on your abdomen feel now?”

- A lot tighter
- A little tighter
- No change
- A little less tight,
- A lot less tight.

STUDY PROCEDURES

PRE-TREATMENT ACTIVITIES
The pre-treatment activities will be conducted at the test site prior to administration of the initial study treatment with the Erchonia® GVS.

SIGNING OF INFORMED CONSENT FORM
The investigator will commence by presenting and reviewing in detail the items in the informed consent form with the individual and answer any questions. To proceed, the individual must willingly sign the informed consent form.

ASSIGNMENT OF SUBJECT ID
The subject will be assigned a unique subject identification number based upon the test site and his or her order of entry into the study.

Additional information about the informed consent and subject ID number assignment is contained in a later section of the protocol titled, “SAFETY AND CONFIDENTIALITY ISSUES.”

STUDY QUALIFICATION EVALUATION: INCLUSION/EXCLUSION CRITERIA

INCLUSION CRITERIA
To be eligible for participation in this study, a subject must satisfy each of the following.

- Subject has signed a written informed consent form.
- Male or female 22 to 70 years of age, inclusive.
- Desire to undergo treatment for skin laxity of the abdomen.
- Subject’s score on the skin laxity scale for skin on the abdomen is 1 (mild) or 2 (moderate).
- Subject agrees to maintain his/her weight (i.e., within 5%) by not making any major changes in diet, exercise or medication routine during the course of the study.
- Subject agrees to refrain from taking any medication(s) or supplements(s), whether prescription or OTC, or undergo any procedures indicated for weight loss, or for fat reduction or improving the appearance of the skin in the abdominal area (e.g. liposuction, ultrasound therapy) for the duration of participation in the clinical study.
- Willing to have research photos taken of treatment areas.
- Understands, and is able and willing to comply with all study visits, treatments and evaluations schedules and requirements.
- Females are at least 9 months post-partum.
- Females are post-menopausal, surgically sterilized, or using a medically accepted form of birth control for at least 3 months prior to the study and agree to continue to do so for the duration of study participation.

EXCLUSION CRITERIA
A subject who satisfies any of the following criteria will be excluded from study participation:

- Skin laxity resulting from genetic disorders, including but not limited to Ehlers-Danlos Syndrome.
- History of undergoing a fat reduction procedure (e.g., liposuction, bariatric surgery, abdominoplasty).
- Botulinum toxin or other aesthetic drug injections within the abdomen area within the past 6 months.

- History of any major prior surgery in the abdominal area
- Implanted medical prostheses (such as clips, pins or plates) in or adjacent to the area of intended treatment.
- Active implanted device such as a pacemaker, defibrillator, or drug delivery system.
- Any clinical and significant dermatological skin condition(s) in the intended abdominal treatment area, such as skin infections or rashes, extensive scarring, psoriasis, etc..
- Tattoo or former tattoo at the treatment area.
- Current moderate to heavy tobacco use, defined as smoking 10 or more cigarettes per day (or equivalent use of other nicotine-containing products such as cigars, pipes, chewing tobacco, or e-cigarettes) within the past 6 months
- History of chronic drug or alcohol abuse.
- Pregnant or intending to become pregnant in the next 6 months.
- Currently enrolled in a clinical study of an unapproved investigational drug or device.

PRE-TREATMENT EVALUATIONS

The following pre-treatment measures will be recorded prior to commencement of the treatment administration phase (prior to treatment administration #1).

BASELINE VARIABLES

- Subject Demographics
- Medications and Procedures
- Diet and Exercise

PRE-TREATMENT OUTCOME ASSESSMENTS

- Body Mass Index (BMI)
  - Height (in)
  - Weight (kg)
- Circumference measurements: waist and hips
- Digital Photographs

TREATMENT ADMINISTRATION PHASE

TREATMENT ADMINISTRATION PROTOCOL

- The treatment administration phase of the study may commence on the same day as the pre-treatment measurements are recorded.
- The treatment administration phase will extend over four consecutive weeks.
- Each subject will receive eight total treatment administrations with the Erchonia® GVS across the consecutive four-week treatment administration phase; two treatment per week; each one at least two days apart.
- Each treatment will take place at the investigator’s test site.
- The treatment administration protocol for each session is as follows:

1. The subject enters the treatment administration room and lays comfortably on a treatment table.
2. The subject is correctly fitted with the safety glasses.
3. The center of the Erchonia GVS treatment head is positioned approximately 4 inches above the subject's abdomen. The GVS treatment head is aligned so that one set of the three central laser diodes is positioned over the left side of the abdomen, while the other set of three central diodes is positioned over the right side of the abdomen.
4. The two adjustable outer arms of the Erchonia GVS are then positioned over the left and

right flanks, respectively, at a distance of approximately 4 inches.

5. The Erchonia® GVS is activated for 30 minutes. Each laser beam will create a spiraling circle pattern that is totally random and independent from the others. These patterns overlap each other to guarantee total coverage within the target area (abdomen).
6. The Erchonia® GVS treatment will run 30 continuous minutes and will stop once treatment time is at 0:00. Once the "Time Remaining" display reaches 0:00 the treatment is complete, and the laser lights and the laser indicator light will turn off.
7. After the Erchonia® GVS is turned off, the subject removes the safety glasses and leaves the treatment administration room.

TREATMENT ADMINISTRATION RECORD

Following the completion of each treatment with the GVS laser, the investigator will record the following:

- Number of treatment administration
- Date
- Investigator signature
- Adverse event (if applicable).

4 WEEK EVALUATION: TREATMENT END

Following the final treatment of the entire 4 weeks of study procedure administrations with the Erchonia® GVS, the following will be recorded on the provided case report forms.

- Review of adherence to medication and procedure use, and diet and exercise regime consistency since pre-treatment visit.
- Digital Photographs
- Circumference measurements: waist and hips
- Global Aesthetic Improvement Scale (GAIS): Investigator and Subject
- Body Mass Index (BMI) Calculation
  - Height (in)
  - Weight (kg)
- Subject Satisfaction with Study Outcome
- Subject-Reported perception of Skin Tightness
- Adverse Events assessment

12 WEEK POST TREATMENT EVALUATION: STUDY EFFICACY ENDPOINT ASSESSMENT

Twelve weeks following the completion of the 4-week treatment administration phase, the following will be recorded on the provided case report forms. These recordings will form the study endpoint data set from which change from baseline will be evaluated with respect to assessing study outcome.

- Review of adherence to medication and procedure use, and diet and exercise regime consistency since prior visit
- Digital Photographs
- Circumference measurements: waist and hips
- Global Aesthetic Improvement Scale (GAIS): Investigator and Subject
- Body Mass Index (BMI) Calculation
  - Height (in)
  - Weight (kg)
- Subject Satisfaction with Study Outcome
- Subject-Reported perception of Skin Tightness
- Adverse Events assessment

STATISTICAL ANALYSIS PLAN

STUDY POPULATIONS
The following two study populations will be evaluated:

1. Intent-to-Treat (ITT) Population

Primary analysis of efficacy will be according to the Intent to Treat (ITT) analysis, including all enrolled subjects.

Missing data for the ITT population will be handled through Last Observation Carried Forward (LOCF) methodology. Sensitivity analysis may be applied if missing data is extensive.

2. Per Protocol Population.

Secondary analysis of efficacy to confirm the findings of the primary analysis will be conducted on the per protocol population, comprised of all subjects who completed the study per protocol through to the final treatment administration and outcomes measures recording visit, without incompletes or major protocol deviations or violations.

3. Safety Analysis Population

The Safety Analysis Population will comprise all subjects who were enrolled in the study.

BASELINE VARIABLES AND RECORDINGS
Descriptive summary data for the following baseline variables and recordings will be provided as numbers (n), mean, standard deviation (SD), median, and range (min., max.) for continuous variables and as number (n) and percentage (%) of the total number for categorical variables.

These variables include:

Subject demographics:
- age
- gender
- race
- ethnicity

Subject recordings:
- Baseline body weight (kg)
- Baseline height (m)
- Baseline Body Mass Index (BMI) in kg/m²
- Baseline waist and hip circumference measurements (ins.)

Medication and Procedures
- Current medications (OTC, prescription) taken for/with weight loss indications
- Prior medications (OTC, prescription) taken for/with weight loss indications
- Procedures undertaken for weight loss indications
- Concomitant medication (OTC, prescription) use for indications other than weight loss

Diet and Exercise
- Daily diet (food and drink consumption)

- Exercise patterns

PRIMARY EFFICACY OUTCOME

Primary study efficacy will be evaluated at 12 weeks post-final treatment relative to baseline (pre-treatment).

The primary efficacy outcome for this study is the change in skin laxity at 12 weeks post-final treatment compared to baseline.

Primary efficacy outcome success will be assessed through Blinded Evaluator assignments of before and after subject digital images from each of Baseline and 12 week follow up visits.

Each of three (3) Independent Blinded Evaluators will be presented with coded, deidentified blinded photograph image sets provided in randomized order post-study endpoint. Each Independent Blinded Evaluator will determine and record which image in the pair they believe to represent the before-treatment image (baseline) and which they believe to represent the after-treatment image (12 weeks follow-up). Additional information about the Independent Blinded Evaluators and the image presentation blinding procedure is contained on page 30 of this protocol under the 'STUDY BLINDING' section.

The primary efficacy endpoint for this clinical study will be considered met if at least 2 of the 3 Independent Blinded Evaluators correctly identify the before-treatment (baseline) and after-treatment (12 weeks post-final treatment) photographs for at least 80% of subjects. That is, the study subject responder rate is ≥80%, with an individual subject responder defined as one whose before- and after-treatment images are correctly identified by ≥2 Independent Blinded Evaluators.

<u>Hypotheses</u>

Therefore, the null and alternative hypotheses for the Primary Efficacy Endpoint are the following:

Null Hypotheses: The overall responder rate will be less than 80%.

H_o: μA < 80%

Alternative Hypothesis: The overall responder rate will be 80% or greater.

H_o: μA ≥ 80%

The rationale for selection of the 80% upper limit for study efficacy outcome success determination is based on the outcome of the various clinical studies used to support FDA clearances for various skin laxity and wrinkle reduction claims, including those for the proposed predicate devices for the current intended submission, where applicable, as well as the highest upper limit typically accepted by FDA, with several other successful clearance-supporting trials establishing and reporting upper limits at 70% and others yielding results in the 60% or lower range.

SECONDARY EFFICACY EVALUATIONS

The following five (5) secondary efficacy evaluations will be performed in support of the primary efficacy evaluation. As no claims are intended to be made based on the secondary efficacy outcomes, the findings will be presented descriptively only as numbers (n), mean, standard deviation (SD), median, and range (min., max.) for continuous variables, and as number (n) and percentage (%) of the total number for categorical variables. Statistical analysis of change will not be performed.

1. *Aesthetic improvement at 4 and 12 weeks post-final treatment compared to baseline*.

Aesthetic improvement at 4 and 12 weeks post-final treatment compared to baseline will be assessed through evaluation of investigator and subject GAIS ratings recorded at each of the respective post-final treatment assessments compared to baseline, with the baseline digital image serving as the baseline reference for determination of post-treatment change. Ratings by subjects and investigator will be assessed separately and in comparison between each other.

2. *Change in circumference measurements at 4 and 12 weeks post-final treatment compared to baseline*.

Change in circumference measurements recorded for each of the hips and waists separately, and combined, at each of 4 and 12 weeks post-final treatment compared to baseline will be assessed.

3. *Change in Body Mass Index (BMI) at 4 and 12 weeks post-final treatment compared to baseline*.

Change in Body Mass Index (BMI) in kg/m²and its constituent component measurements of height (m) and body weight (kg) at each of 4 and 12 weeks post-final treatment compared to baseline will be assessed.

4. *Subject Satisfaction with Treatment Outcome Ratings at 4 and 12 weeks post-final treatment*. Subject satisfaction with treatment outcome ratings recorded at each of 4 and 12 weeks post-final treatment will be assessed and compared.

5. *Subject-Reported perception of Skin Tightness at 4 and 12 weeks post-final treatment.* Subject-Reported perception of Skin Tightness outcome ratings recorded at each of 4 and 12 weeks post-final treatment will be assessed and compared.

COVARIATE/SUBGROUP ANALYSIS

The impact of the following potential covariates on the primary study efficacy outcome may be evaluated, as indicated:

- Age
- Gender
- Ethnicity
- Race
- Baseline height (m)
- Baseline body weight (kg)
- Baseline BMI (kg/m²)
- Baseline waist circumference measurement (in)
- Baseline hips circumference measurement (in)

ADDITIONAL CONSIDERATIONS
Depending on the variations identified, a discussion on the potential impact of variability in subject reported use of medications and procedures, and diet and exercise patterns at baseline assessment may occur.

SAFETY ANALYSES
Safety will be assessed by evaluating observed and/or reported adverse events.

ADVERSE EVENTS

At each evaluation and measurement point throughout the clinical study, and at any other time throughout the duration of the clinical trial that is necessary, all potential adverse events reported by a subject or observed by an investigator will be recorded on the case report form, and subsequently evaluated by the investigator for its relation to the study procedure and whether any corrective action needs to be taken. All potential adverse events recorded will be appropriately reported to the governing IRB, as applicable.

It is unlikely and not expected that any adverse events will result from implementation of this clinical study protocol. Prior clinical trials using low level laser light, including the prior Erchonia clinical study evaluating the Erchonia green and violet laser combination, have not typically yielded any adverse events or reactions. However, potential adverse events that may feasibly occur from application of the Erchonia® GVS include, but are not necessarily limited to skin irritation, discoloring, rash, indentations, and infection.

ADVERSE EVENTS DEFINITION

An 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 (a)).

SERIOUS ADVERSE EVENTS (SAE) DEFINITION

An adverse event (AE) 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 subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

It is not anticipated that any SAE will occur from participation in this study.

UNANTICIPATED ADVERSE DEVICE EFFECT (UADE) DEFINITION

An unanticipated adverse device effect is defined as any serious adverse effect on health or safety, or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence

in the investigational plan, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects."

CLASSIFICATION OF AN ADVERSE EVENT

A. Severity of Event

All AEs will be graded for severity by the study investigator according to the following grading system definitions.

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

B. Relationship to Study Intervention

All AEs will have their relationship to the study intervention assessed by the study investigator who examines and evaluates the subject based on temporal relationship and his/her professional clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related:** There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event occurs in a plausible time relationship to study capsule administration and cannot be explained by concurrent disease, medications, or other treatments.
- **Probably Related:** There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event occurs within a reasonable time after administration of the study capsule, is unlikely to be attributed to concurrent disease, medications, or other treatments.
- **Not Related:** The AE is completely independent of study capsule administration, and/or evidence exists that the event is definitely related to another etiology. The alternative, definitive etiology must be fully documented by the clinician.

C. Expectedness

The study 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 intervention.

An AE will be considered **expected** if the nature, severity, or frequency of the event is consistent with the risk information previously described for the study intervention.

TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or serious adverse event (SAE) may come to the attention of study

personnel during study visits and interviews of a study subject presenting for medical care, or upon review by a study monitor.

An **unsolicited AE** is defined as one that is reported without specific prompting or in response to a general question.

A **solicited AE** is one that is specifically solicited through asking a question regarding a specific potential AE.

Reporting and data collection for an AE will distinguish if a captured AE was unsolicited or solicited.

AEs will be collected throughout study duration.

REASONABLY ANTICIPATED AND POTENTIAL ADVERSE EVENTS

SAEs are not anticipated to occur in this clinical study.

There are no anticipated adverse events in this clinical study.

Potential adverse events that may feasibly occur from application of the Erchonia® GVS laser device include, but are not necessarily limited to skin irritation, discoloring, rash, indentations, or infection.

ADVERSE EVENT RECORDING

All AEs that occur, including local and systemic reactions, not meeting the criteria for SAEs will be captured on the appropriate AE case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), corrective action taken, time of resolution/stabilization of the event and if the subject was withdrawn from the study because of the AE. Recording will be done in a concise manner using standard, acceptable medical terms.

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 subject is screened will be considered as baseline and not reported as an AE. However, if the study subject's condition deteriorates at any time during the study, it will be recorded as an AE.

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 study investigator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation.

Events will be followed for outcome information until resolution or stabilization.

ADVERSE EVENT REPORTING

Adverse Event Reporting Timeframes

The table below lists the minimum AE reporting requirements for study Investigators. Reporting of all safety events to the Sponsor will be completed through Investigator submission of the AE CRF and any applicable supporting documentation

Table 1: Investigator AE Reporting Requirements

Type of AE	Report to	Reporting Timeframe (from time of learning of event)
Adverse Event (AE)	IRB	Per IRB reporting requirements
	Sponsor	Within 10 working days
Serious Adverse Event (SAE)	Sponsor	Within 24 hours
	IRB	Per IRB reporting requirements
Device Deficiency	Sponsor	Within 48 hours
	IRB	If SAE occurs due to the device deficiency, within 24 hours of learning of the event and per IRB reporting requirements
Device Related AE/SAE	Sponsor	Within 24 hours

Unanticipated Adverse Device Effect (UADE) Reporting

The study investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the sponsor and to the reviewing Institutional Review Board (IRB) a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect (21 CFR 812.150(a)(1)). A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to the FDA and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests (21 CFR 812.150(b)(1)).

An unanticipated adverse device effect will be added to the subject informed consent form under IRB approval. No new subject will be enrolled in the study until after the change has been made to the consent form. Therefore, all subsequent potential subjects will be made aware of the unanticipated problem prior to deciding on study participation. Subjects who have already completed the study will not be informed about the occurrence of an unanticipated problem unless it is determined to have occurred after study completion.

Reporting Events to Subjects

An occurring AE or SAE not already captured as a potential risk of study participation in the subject informed consent document will be added to the consent form under IRB approval. No new subject will be enrolled in the study until after the change has been made to the consent form. Therefore, all subsequent potential subjects will be made aware of the new AE or SAE prior to deciding on participation.

Subjects who have already completed the study will not be informed about newly occurring AEs or SAEs unless the AE or SAE is determined to have occurred after study completion.

UNANTICIPATED PROBLEMS (UP)

Unanticipated Problems (UP) Definition

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets **each** 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 Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the subject 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 subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

PRIVACY AND CONFIDENTIALITY

REGULATORY, ETHICAL, AND STUDY OVERESIGHT CONSIDERATIONS

Informed Consent Process

An informed consent form (in written paper or in electronic format) describing in detail the study intervention, study procedures, and risks is given to each subject and written or electronically captured with identity verification documentation of informed consent is required prior to the subject starting any study activities, including study qualification evaluation. There are no other consent documents provided to subjects in this study.

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. Consent forms will be IRB-approved, and the subject will be asked to read and review the document. The investigator will explain the research study to the subject and answer any questions that may arise. A verbal explanation will be provided in terms suited to the subject's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research subjects. Subjects will have the opportunity to carefully review the written consent form and ask questions prior to signing. The subjects will have the opportunity to take the consent form home, and to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The subject will sign the informed consent document prior to any procedures or activities being done specifically for the study. Subjects will be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the subject for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed by both the subject and the site staff member who reviewed the consent form with the subject before the subject undergoes any study-specific procedures or activities. 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.

- Informed consent will be an agreement between the individual investigator and each subject, having the capacity to understand and make an informed decision. Consent will be obtained prior to each potential subject's participation in this clinical study.
- Each subject participating in this clinical study will be made aware of the fact that his or her participation involves research and the intent of the research, the expected duration of his or her participation and a description of the procedures that will be followed.
- Each subject will be made aware of the reasonably expected benefits he or she might receive, as well as any risks or potential discomfort that are involved.
- Each subject will also be made aware of alternative treatments available to him or her.
- Each subject will be made aware that his or her records will remain confidential, but that the FDA and the IRB has the right to inspect his or her records.
- Each subject will be told that his or her participation in the clinical study is voluntary, without force or influence from the investigator or sponsor.
- Each subject will be given the name and method of contacting the appropriate person(s) to answer his or her questions about the research and in the event of a research-related injury.

The informed consent form that will be used to collect the data from each subject in this clinical study can be found in **Appendix E.**

Confidentiality and Privacy

Subject confidentiality and privacy are strictly held in trust by the participating investigators, study staff, and the sponsor(s) and their interventions. 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.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB, or regulatory agencies may inspect all documents and records required to be maintained by the investigator for the subjects in this study. The clinical study site will permit access to such records.

Records for each subject in this clinical study will be maintained in separate files in a locked filing cabinet at the test site. The investigator at the test site will be responsible for ensuring that all records for a subject pertaining to his or her participation in the clinical study are always stored in that subject's file other than when information is being recorded on them.

The study Monitor will have access to the files for the purposes of data monitoring and auditing. Once the study is complete, copies of each of the subject case report forms will be made and supplied to the study statistician for analysis of results. The study statistician will maintain these copies in a separate clinical study file that is kept in a locked filing cabinet on their premises. The original records will be maintained at the respective test sites upon completion of the study in their original files and stored in a locked filing cabinet.

Subjects' identities will be kept confidential by assigning each subject a unique de-identified subject ID upon acceptance into the study as explained above. Paper consent forms containing subject names and signatures will be maintained in separate folders stored in a separate locked location from the subject binders such that no association between a subject's name and his or her Subject ID can be formed.

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 the FDA, reviewing IRB, Institutional policies, or sponsor requirements.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This web site will not include any identifiable information for subjects. At most, the web site will include a summary of the study results.

QUALITY ASSURANCE AND STUDY MONITORING

STUDY DATA MONITORING

The study sponsor will be responsible for monitoring the study sites to review the data being collected. The sponsor shall implement and maintain quality control and quality assurance procedures with written standard operating procedures (SOPs) to ensure that the trial is being conducted and data are generated, documented, and reported in compliance with the protocol, Good Clinical Practice (GCP) and applicable regulatory requirements.

The investigator agrees to allow the monitor and other authorized personnel direct access to source data/documents for trial related monitoring, the clinical supplies storage/dispensing area and to provide all documents in the Investigator Regulatory File (or Site Regulatory Binder) for review, and to assist site auditors in their activities if requested. Requests by the FDA to inspect the study site may be made after adequate notification. The investigator may be required to assist the regulatory inspectors in their duties, if requested.

A Clinical Trial Monitoring Plan will be in place to ensure on-going compliance and accuracy of procedures throughout the trial.

QUALITY ASSURANCE AND QUALITY CONTROL

The clinical site will perform internal quality management of study conduct, and data collection, documentation, and completion per the site's SOP and quality management plan.

Quality control (QC) procedures will be implemented beginning with data entry and data QC checks that will be performed on the recorded data. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted, and data are generated, and documented (recorded) in compliance with the protocol, ICH GCP, and any other applicable regulatory requirements.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

DATA HANDLING AND RECORD KEEPING

Data Collection, Recording and Management Responsibilities

Study documents pertaining to data collection will be developed by the sponsor to record all study data and assure compliance to the protocol. All data collection documents will be tracked and monitored for completion and accuracy by sponsor-assigned monitor(s).

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Case Report Forms

The case report forms that will be used to collect the data from each subject in this clinical trial can be found in **Appendix D.**

Data Confidentiality

All physical copies of subject medical records, source and other research documents will be stored in secure cabinets at the study site. All such study documentation containing subject information will be identified by the de-identified coded subject ID only. There will be no identifying information included on any subject CRFs or other source documentation, per HIPAA. Subject confidentiality will be protected to the greatest extent possible.

Study Records Retention

The investigator is responsible for retaining a copy of all study records for three (3) years after the study is completed or terminated. All original study data will be retained by the sponsor for no longer than five (5) years after the study is completed or terminated.

PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, ICH GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents (CRFs) and be reported to the sponsor. Protocol deviations must be sent to the reviewing IRB as applicable per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

The investigator will not intentionally deviate from the study protocol procedures except in medical emergencies. Any and all protocol deviations that do occur will be recorded on the CRF and the IRB will be informed of the deviation, if applicable.

Protocol deviations will be recorded in CRFs and monitored for completion and accuracy during each monitoring visit.

SUBJECT SAFETY MONITORING

Subject safety data will be recorded in CRFs and monitored for completion and accuracy during each monitoring visit.

Subjects will be asked about any adverse events at the test site and are required to record any

potential adverse events in the Adverse Events Record Form and to notify the test site immediately. In such an occurrence, an unscheduled visit may be arranged so that the Investigator can clinically evaluate the findings. All adverse events will be recorded and reported as per the plan described in the relevant section above.

The Investigator can decide to stop the subject's participation in the study if he/she believes that subjects' participation is no longer safe.

The sponsor or the IRB may stop the research for the safety of the subjects if unreasonable risks to subjects persist.

PROTOCOL AMENDMENTS

Any amendments required to the clinical study protocol will be submitted for approval to the IRB before implementation. Subjects will be re-consented for these amendments as applicable.

END OF DOCUMENT