ERCHONIA® PPL

An Evaluation of The Erchonia® PPL Laser as a Pre-Treatment Adjunct to Enhance Standard Erchonia Red Laser Therapy for the Temporary Relief of Nociceptive Musculoskeletal Pain

ERCHONIA CORPORATION

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STUDY INFORMATION

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PURPOSE OF STUDY
The purpose of this clinical study is to evaluate whether pre-treatment with the Erchonia® PPL blue laser therapy, followed sequentially with the standard Erchonia red laser therapy, is non-inferior to (equivalent to or superior to) the standard Erchonia red laser therapy when applied alone in providing temporary relief of nociceptive musculoskeletal pain.

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

"The Erchonia® PPL is indicated for use as a pre-treatment adjunct to enhance the standard Erchonia red laser therapy for the temporary relief of nociceptive musculoskeletal pain."

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

EXPECTED RESULTS
Following completion of the treatment protocol involving the Erchonia® PPL laser applied prior to the standard Erchonia red laser therapy, it is anticipated that subjects will experience outcomes comparable (equivalent to) or superior to those achieved with Erchonia red laser therapy alone for the temporary relief of nociceptive musculoskeletal pain. Specifically, improvements will be assessed based on reductions in neck and shoulder nociceptive pain intensity as measured using the 0–100 Visual Analog Scale (VAS) at the study endpoint relative to baseline.

REGULATORY BACKGROUND
Erchonia Corporation, the manufacturer of the PPL Laser, has an extensive regulatory history with the U.S. Food and Drug Administration (FDA) in the field of low-level laser therapy (LLLT). The safety and efficacy of Erchonia's red diode laser devices—regulated under FDA Product Code NHN—are well established through multiple controlled clinical trials. These devices have received FDA 510(k) clearance for adjunctive use in various musculoskeletal pain indications, including:

- Chronic heel pain associated with plantar fasciitis (K132940)
- Chronic neck and shoulder pain of musculoskeletal origin (K012580)
- Chronic low back pain of musculoskeletal origin (K180197)

In recognition of the reproducible therapeutic effects of Erchonia red diode lasers across multiple anatomical regions, including those demonstrated in the above referenced clearances and supportive clinical data, the FDA granted Erchonia red diode lasers a generalized clearance for:

- **Adjunctive use in providing temporary relief of nociceptive musculoskeletal pain (K190572 & K212595)**

Erchonia has also demonstrated the clinical utility of other visible laser wavelengths, such as violet, which is spectrally adjacent to the blue wavelength utilized in the PPL Laser. These additional devices have been cleared under the same NHN product code and include:

- K221987: Simultaneous use of green and violet diode lasers for adjunctive temporary relief of minor chronic neck and shoulder pain of musculoskeletal origin
- K191257: Simultaneous use of red and violet diode lasers for adjunctive temporary relief of minor chronic neck and shoulder pain of musculoskeletal origin
- K212585: FX-405 (red and violet) Laser for adjunctive temporary relief of nociceptive musculoskeletal pain

Building upon this extensive clinical and regulatory foundation, Erchonia Corporation has developed the PPL Laser, which emits a low-powered blue wavelength. The PPL Laser is intended for use as a pre-treatment adjunct to the standard red laser therapy, with the goal of enhancing therapeutic outcomes in patients with nociceptive musculoskeletal pain.

This clinical study protocol is modeled closely after Erchonia's previous study that supported FDA market clearance for the red laser device (PL3000 cleared under K012580) indicated for "adjunctive use in providing temporary relief of minor chronic neck and shoulder pain of musculoskeletal origin." The key distinction in this protocol is the inclusion of a 5-minute pre-treatment protocol using the Erchonia PPL Laser—delivering low-level blue diode light to the neck and shoulder region—followed by a 13-minute application of the standard Erchonia red diode laser therapy.

For the red laser application, this study will utilize the Erchonia XLR8 device, which represents the current generation of Erchonia's red laser systems. The XLR8, cleared under K211186 for the same IFU of *"adjunctive use in providing temporary relief of minor chronic neck and shoulder pain of musculoskeletal origin"* has been determined to be substantially equivalent to its Erchonia predecessor models—including the PL3000, originally cleared under K012580.

DEVICE INFORMATION : ERCHONIA® PPL

DEVICE DESCRIPTION & DETAILS

The Erchonia® PPL is a non-thermal, non-invasive low-level laser device designed to be administered prior to administration of the standard Erchonia red laser therapy for the adjunctive temporary relief of nociceptive musculoskeletal pain. The handheld device utilizes two patented electronic semiconductor diodes emitting visible blue light at a wavelength of 450 nanometers, each with a power output of 8.75 mW.

The system is classified as a Class II laser under IEC 60825-1 and is compliant with 21 CFR 1040.10 and 1040.11, as modified by Laser Notice No. 50. Powered by an internal rechargeable battery, the PPL recharges via an inductive charging base using an external Class II medical-grade power supply compatible with 120V/60Hz and 220V/50Hz AC mains power. A built-in touchscreen interface serves as both a control panel and display, communicating directly with the internal printed circuit board (PCB) to initiate or pause laser emission.

The PPL system is preprogrammed with variable Hertz settings, comprising a series of controlled modulation patterns. There is no user-accessible interface to modify output power or wavelength, ensuring consistent, reliable, and safe laser energy delivery. This configuration offers both portability and precision in therapeutic application.

The Erchonia® PPL has the following specifications:

Device
- Weight: .66lbs / *.30kgs*. Charger Base-.60lbs / *.27kgs*
- Full Color TFT Touch Screen Module
- Machined billet aluminum enclosure
- Dimensions: Length-6.8” (*17.27cm*) Width-3.10” (*7.87cm*) Depth-.75” (*1.90cm*), Charger Base- Length-5.36” (*13.61cm*) Width-3.86” (*9.80cm*) Depth (adjustable)-2.18” – 4.35” (*5.54cm – 11.05cm*)

Light Diodes
- 2 electronic diodes, with patented optics
- Output: 10mW
- Wavelength: 450nm

Power
- Battery: Lithium-ion Polymer 3.7V, ≤3000mAh, 6.7W

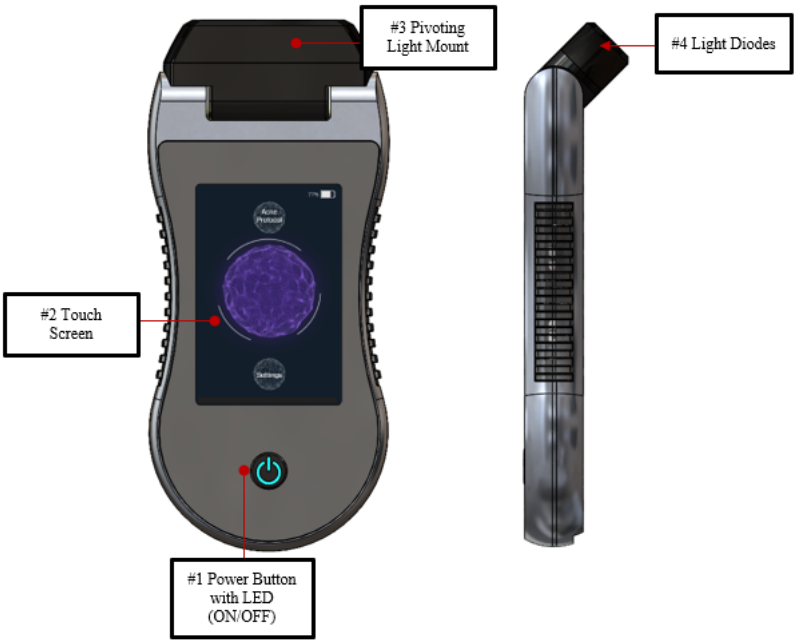
Inductive Charging Base
- 1.2A 15V

External Power Supply
- Model: ER-E-00375
- 100-240Vac, 47-63Hz, 0.5A; 15Vdc 1.2A

The following diagram identifies each component of the device, and a complete description of the component follows.

#1 POWER BUTTON WITH LED (ON/OFF)

The Power Button allows the user to turn the device ON "|" or OFF "O". To turn the device ON, the Power Button is pressed and released to activate the blue power LED.



#2 TOUCH SCREEN

The touch screen functions as a display screen and an input panel, providing information and a means to operate the device by touching the appropriate icon.

#3 PIVOTING LIGHT DIODE MOUNT

The Pivoting light diode mount allows the user to adjust the light diode angle 90 º in one direction and 45 º in the other direction.

#4 LIGHT DIODES

The device consists of two electronic light diodes, with patented optics. These light diodes, when activated, emit blue beams.

DEVICE SAFETY

RISK AND PREVENTION OF EYE INJURY

The Erchonia® PPL 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 subject. 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, eye protection is implemented for the subject receiving the laser procedure administrations.

A pair of safety glasses is provided for use during all procedure applications. These safety glasses are Noir laser shields. The safety glasses sufficiently and effectively block the laser light spectrum at OD 6+ @ 190-534nm, VLT 7%.

- Height: 47 mm
- Width: 130 mm
- Length: 130 mm

OTHER POTENTIAL RISKS

Other potential risks and their mitigation include:

(i) Electric shock: operator risk only: mitigated through electrical safety testing.
(ii) Electromagnetic interference: mitigated through EMC/EMI testing.
(iii) User error: mitigated through instructions for use documentation.

LABELING

The Erchonia PPL 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.

STUDY INDICATION, THEORY OF MECHANISM OF OPERATION, SUPPORTING MATERIALS, AND STUDY JUSTIFICATION

STUDY INDICATION: NOCICEPTIVE MUSCULOSKELETAL PAIN

Nociceptive pain is the most common type of pain experienced and refers to pain caused by physical damage or potential damage to the body, such as from a sports injury, or arthritis. It develops when the nociceptive nerve fibers are triggered by inflammation, chemicals, or physical events. The body contains specialized nerve cells called nociceptors. A nociceptor is a sensory neuron that responds to damaging or potentially damaging stimuli by sending "possible threat" signals to the spinal cord and the brain. If the brain perceives the threat as credible, it creates the sensation of pain (nociceptive pain) to direct attention to the body part, so the threat can hopefully be mitigated; this process is called nociception. (Premkumar and Sikand 2008; Mandadi and Roufogalis 2008; Hsiao et al. 2008; Stucky et al. 2009; Ranoux 2008; Price et al. 2009). Current treatment options for nociceptive pain focus on pain management including rest, heat and ice pads, immobilization and compression, physical therapy, use of pain-relieving medications, and low-level laser light therapy.

Any tissue damage to the body triggers nociception and causes nociceptive pain, including damage to bones, joints, ligaments, tendons, muscles, organs, and skin that may occur due to physical trauma such as an injury (e.g. broken bones, sprains and strains) or surgery, or from inflammation due to chronic conditions such as arthritis.

- One common type of nociceptive pain is nociceptive musculoskeletal pain arising from impairment of the muscles, ligaments and tendons, and bones. The American Academy of Pain Medicine reports that over half (53%) of the U.S. workforce reports some form of musculoskeletal pain at any one time, and about 13% lost productive work time averaging 5.5 hours per week while experiencing musculoskeletal pain.

Prominent within this realm is nociceptive pain of musculoskeletal origin located in the neck and shoulders that is generally chronic in nature, meaning it persists for most days of the month over at least one month. The National Institute of Health Statistics survey reports chronic neck pain as being the second most common pain complaint (second to low back pain), experienced by 15% of the U.S. adult population at any one time. Per the American Academy of Pain, chronic pain is reported to have a significant impact on quality of life, with 59% of those afflicted reporting an impact on overall enjoyment of life; 77% reporting feeling depressed; 70% reporting trouble concentrating; 74% reporting reduced energy level; and 86% reporting sleep disruption.

Neck and Shoulder Nociceptive Musculoskeletal Pain

The spine can be compartmentalized into three (3) separate sections: the neck, the mid back and the low back. The neck refers to the cervical spine, which is comprised of the top seven (7) vertebrae, the vertebral joints which connect them, and the ligaments and muscles that provide neck stability, function, and movement. Impairment therein primarily results in pain and reduced range of motion in the neck and shoulders region.

Causes of musculoskeletal neck/shoulder pain include muscle tissue damage due to wear and tear from daily activities; trauma (jerking movements, auto accidents, falls, fractures, sprains, dislocations, and direct blows to the muscle); postural strain; repetitive movements; overuse and prolonged immobilization.

In this clinical study, the most common cause of chronic neck/shoulder nociceptive pain is being evaluated, that of **the musculoskeletal conditions of muscle sprain, strain and spasms of the neck and/or shoulder region.**

Muscle Strain, Sprain and Spasm of Musculoskeletal Origin

Muscle strain, sprain and muscle spasm of musculoskeletal origin refers to damage to a muscle or its attaching tendons due to undue pressure placed on muscles during the course of normal daily activities, including those that involve sudden heavy lifting, sports activities or other physical exertions, or while performing work tasks. Muscle damage can involve tearing of some or all of the muscle fibers and the tendons attached to the muscle. This tearing can also damage small blood vessels, causing local bleeding, or bruising, and pain caused by irritation of the nerve endings in the area.

Muscle sprain and strain occurs with a sudden stressful injury to the region causing stretching or tearing of the muscle/tendons/ligaments resulting in pain and restricted range of motion. 'Sprain' refers to injury of the muscles, whereas 'strain' refers to injury of the ligaments.

The muscles and ligaments in the neck and shoulder regions are part of the body's upper extremity. The upper extremity is innervated by nerves originating in the cervical and thoracic spine. Sprain strain in the neck and/or shoulder regions refers to an injury that causes a sprain to a muscle or strain to a ligament that affects pain and restricts range of motion in those areas that is linked to degraded integrity of the accompanying cervical and thoracic nerve supply.

In a muscle strain, the tension or extreme stretching that occurs causes the muscles to cramp or tear during physical exertion. Efforts to move are then replaced by painful and limited movement. The pain of muscle strain or spasms arises from the sustained contraction of the muscle fibers, as well as from possible tearing of the fibers which may be felt as a hard knot in the strained muscle.

Chronic muscle spasms (also known as muscle cramp, -pulled" muscle, or tight muscle) are an indirect injury to a muscle, usually from muscle fatigue and overuse that results from involuntary contractions of a muscle or a group of muscles causing pain and interference with function.

Neck and shoulder spasms are involuntary contractions of the muscles in the neck and shoulders wherein the muscles get tight, hard, and painful. Neck spasms most commonly result from injury, overuse, poor posture, or stress

Common types of physical activity or exertion that may result in muscle strain/sprain/spasms and resultant pain in the neck and shoulder include running, climbing, extreme reaching with the arms, or turning/twisting of the head, neck, or back, as well as prolonged work in poorly ergonomically designed work-related settings, requiring holding the neck or back in an abnormal position or posture while seated for prolonged periods.

Symptoms

Primary symptoms of muscle strain/sprain/spasms of musculoskeletal origin include*:*

- pain and soreness in the neck/shoulders that worsens with movement
- neck/shoulder stiffness, tightness and weakness
- limited range of motion of the neck/shoulders

Additional potential symptoms include headaches, tender or trigger spots in the neck/shoulder, a hard knot tender upon palpation, fatigue, and sleep disturbances.

Diagnosis

Diagnosis of neck/shoulder muscle strain/sprain/spasms of musculoskeletal origin involves a comprehensive medical and patient history and physical examination, and possible diagnostic evaluation (e.g. lab tests, imaging studies such as x-rays, CT scan, MRI, and myelogram).

Treatment Options

Current available treatment options include

rest, ice and heat application, compression, immobilization, use of pain-relief and muscle relaxant medications, physical therapy, low-level laser light therapy, chiropractic care, and acupuncture.

THEORY OF MECHANISM OF OPERATION OF THE APPLICATION OF THE ERCHONIA PPL AS AN ADJUNCT TO ENHANCE THE STANDARD RED LASER THERAPY FOR THE TEMPORARY RELIEF OF NOCICEPTIVE MUSCULOSKELETAL PAIN AND FOR THE TEMPORARY RELIEF OF CHRONIC NECK AND SHOULDER PAIN OF MUSCULOSKELETAL ORIGIN

Erchonia Corporation currently has FDA 510(k) clearance for the following indication for use:

"adjunctive use in providing temporary relief of nociceptive musculoskeletal pain,"

… both when using the standard red laser therapy alone (K190572) and when using a simultaneously administered violet and red laser therapy combination (K212595).

Additionally, Erchonia Corporation has numerous FDA 510(k) clearances for the following indication for use:

"adjunctive temporary relief of minor chronic neck and shoulder pain of musculoskeletal origin,"

… both when using the standard red laser therapy alone (K012580, K130996, K100509, K130741, K152196, K211186); when using a simultaneously administered green and violet laser therapy combination (K221987); and when using a simultaneously administered red and violet laser therapy combination (K191257).

As such, Erchonia has previously demonstrated the theory of mechanism of operation to the FDA's satisfaction regarding application of red laser light therapy for adjunctive use in providing temporary relief of nociceptive musculoskeletal pain, and additionally for the specific source of nociceptive musculoskeletal pain of minor chronic neck and shoulder pain of musculoskeletal origin. Therefore, this information will not be reiterated in this protocol in the detail to which it was presented in the prior respective clinical trial protocols.

However, although the Erchonia laser in combination violet and red diode administration is 510(k) cleared for both adjunctive use in providing temporary relief of nociceptive pain and specifically of minor chronic neck and shoulder pain of musculoskeletal origin, this study involves application of the Erchonia laser using *blue* (not violet) and red light, with the blue light therapy *preceding* (not occurring simultaneously with) the red light therapy. Therefore, the following mechanism of action is proposed, building on that already accepted by FDA for red light only administration and simultaneous violet/red light combination administration.

Overall, LLLT is effective in reducing nociceptive pain, because it reduces the nociceptive information traveling the neural pain networks, producing an increase in nociceptive threshold that results in neural blockade, specifically an inhibition of A and C neural fibers. This inhibition may be mediated by altering the axonal flow (or by inhibiting neural enzymes).

Specifically in consideration of the red visible light spectrum, Erchonia Low-level Laser Therapy (LLLT) has been shown to exert its therapeutic effects primarily through mitochondrial activation. Red photons penetrate the tissue and are absorbed by cytochrome c oxidase (CCO), a key enzyme in mitochondrial complex IV located on the inner mitochondrial membrane. Absorption of this light energy enhances electron transport activity, promotes oxidative phosphorylation, and increases the production of adenosine triphosphate (ATP), the primary energy currency of the cell.

This bioenergetic enhancement initiates several downstream effects:

- Activation of energy-dependent enzymes
- Increased synthesis of growth factors (e.g., VEGF, NGF, FGF)
- Enhanced protein production and cell proliferation
- Greater tissue repair
- Modulation of pain through β-endorphin release
- Improved immune function via increased lymphocyte activity

To further improve treatment efficacy, this protocol introduces a blue light pretreatment phase prior to application of the proven standard red laser therapy. The blue laser light is spectrally adjacent to the violet laser light which, as outlined above, has already been proven to enhance the effect of the red laser light therapy when administered simultaneously. Blue light specifically targets the outer cell membrane and influences mitoNEET, a regulatory protein located on the outer mitochondrial membrane. MitoNEET exhibits peak absorption in the blue wavelength range and plays a crucial role in maintaining mitochondrial function, redox balance, and energy regulation.

When mitoNEET is dysfunctional, it disrupts the transfer of iron–sulfur (Fe–S) clusters, impairs substrate oxidation, and alters mitochondrial redox signaling. These impairments can cause cells to shift from high-efficiency ATP production via oxidative phosphorylation to glycolysis, a low-efficiency pathway yielding only ~2 ATP per glucose compared to ~36 ATP through oxidative phosphorylation. This metabolic reprogramming bypasses the electron transport chain (ETC), undermining the effectiveness of traditional LLLT therapies which depend on ETC activation for therapeutic benefit. By pre-targeting the treatment area with blue light, the cellular environment is optimized, supporting mitoNEET function and preserving mitochondrial integrity. This ensures that the subsequent red laser therapy can effectively stimulate the ETC and restore efficient ATP production, maximizing therapeutic outcomes in nociceptive musculoskeletal pain relief.

SUPPORTING ERCHONIA CORPORATION CLINICAL DATA

1. The following Erchonia-sponsored clinical study outcome supported the 510(k) clearance for application of Erchonia *red laser light therapy alone* to the *adjunctive temporary relief of minor chronic neck and shoulder pain of musculoskeletal origin.*

CHRONIC NECK AND SHOULDER PAIN:
Low-Level Laser Therapy for the Treatment of Chronic Neck and Shoulder Pain Funct Neurol Rehabil Ergon 2016;6(2):97-104. Gregory C. Roche; Daniel J. Murphy ...

This pivotal study was a prospective, multi-center, randomized, double-blinded placebo controlled dual-arm study of 100 subjects, of which 86 passed screening and were available for primary endpoint analysis. Subjects were adults with neck and shoulder pain of musculoskeletal origin (osteoarthritis, chronic muscle spasms and cervical and thoracic spine sprain strain) ongoing for at least 30 days with a recorded 0-100 VAS pain scale rating of 50 or greater. Average duration of neck and/or shoulder pain at study entry was about 6 years. Red laser light therapy was administered to the sagittal suture (top of head); left and right cervical, shoulder and torso areas; right and left shoulders during each of passive external rotation and passive adduction of the arm and shoulder; right and left cervical muscles and trapezius muscles during passive left lateral flexion of the cervical spine; and the right and left sternocleidomastoid and scalene muscles during passive range of motion, for a total of 13 minutes during a single treatment administration. Post-treatment follow-up period was 48 hours.

Primary efficacy success was evaluated immediately following the single device treatment administration relative to baseline as the change in neck and shoulder pain rating as recorded on the 0-100 VAS. Individual subject success was defined as a 30% or greater improvement (decrease) in the primary efficacy measure from baseline to endpoint. Study success was defined as a minimum 30% difference between treatment groups, comparing the proportion of individual successes. 65.1% of actively treated subjects attained individual success compared with 11.6% of control (placebo) subjects, resulting in a 53.5% difference between treatment groups, exceeding the 30% criteria by 23.5% ($p<0.0001$). Hence the study met its primary efficacy endpoint. Additionally, the magnitude of the mean change in neck and shoulder pain VAS rating at endpoint relative to baseline was -29.02 for actively treated subjects and -4.91 for control (placebo) subjects, a 20.08 difference ($p<0.0005$). No treatment-related adverse event was reported or observed for any subject throughout study duration, and no other safety issues occurred.

2. The following Erchonia-sponsored clinical study outcome supported the 510(k) clearance for application of the simultaneous *combined Erchonia red and violet laser light therapy* to the *adjunctive temporary relief of minor chronic neck and shoulder pain of musculoskeletal origin.*

The study was a single (active treatment only) group non-inferiority design to evaluate equivalency or superiority of the Erchonia® EVRL in red/violet diode combination application with red diode only application in the temporary reduction of neck and shoulder pain of musculoskeletal origin. The comparative active data for the Erchonia® red diode only therapy was attained in the 2001 trial whose results successfully supported 510(k) clearance (K012580) of application of the PL3000 red diode only for the identical indication being sought through the results of this clinical trial.

Forty-four (44) subjects completed the study. Subjects were predominantly Caucasian (82%) males (39%) and females (61%) of average age 54.07 years with chronic neck and/or shoulder pain of musculoskeletal origin due to osteoarthritis, chronic muscle spasms or cervical and thoracic spine sprain strain who rated 50 or greater on the 0 to 100 Visual Analog Pain Scale (VAS). Average subject duration of neck and shoulder pain was 76.58 months with the location of pain evenly distributed across the right and left sides. Average VAS pain rating at study entry

was 65.00. In the 2001 comparative trial, 43 subjects received the active Erchonia® EVRL red diode only procedure administration.

Each subject received a single 13-minute active procedure administration with the Erchonia® EVRL at the investigator's test site as in the 2001 trial, differing only in dual-diode (red and violet) versus single-diode (red only) application, respectively.

Study primary outcome measure was change in Visual Analog Scale (VAS) neck and shoulder pain rating from baseline to study endpoint evaluation. Individual subject success criteria was established as a 30% or greater decrease in VAS rating at endpoint relative to baseline. The study was pre-established as a non-inferiority study (equivalency or superiority) of the EVRL in red/violet diode combination therapy compared to the red diode only therapy as based upon the comparative data from the 2001 trial. Overall study success criteria was established as 65±5% of individual subject successes in the current trial. Seventy-five per cent (75%) of subjects in this dual diode violet/red laser study attained individual subject success compared with 65.1% of actively treated subjects in the 2001 trial, exceeding the overall study success criteria by 5%. The 29.80-point mean decrease (from 65.00 to 35.20) in neck and shoulder VAS pain rating from study Baseline to Endpoint for subjects in the violet/red laser study was comparable to (slightly above) the respective 29.02-point mean decrease (from 60.21 to 31.19) for the 2001 Active study subjects. As in the 2001 red laser only study, no adverse or other safety events were reported or recorded across study duration.

It was concluded that the application of simultaneous violet and red laser light was non-inferior to the application or red laser light alone in providing adjunctive temporary relief of minor chronic neck and shoulder pain of musculoskeletal origin.

3. The above two Erchonia-sponsored clinical trial outcomes, in addition to the below two Erchonia-sponsored clinical trial outcomes provided primary support for clearance of the indication for '*adjunctive use in providing temporary relief of nociceptive musculoskeletal pain'* for the respective light therapy devices:

   - CHRONIC LOW BACK PAIN:
     Trevor S B, Travis M S, Steve S. Two Randomized, Double Blind, Placebo-Controlled Trials Evaluating the Efficacy of Red 635nm Low Level Laser for the Treatment of Low Back Pain. Ortho & Rheum Open Access J. 2021; 17(3): 555964 10.19080/OROAJ.2021.17.555964

   - CHRONIC PLANTAR FASCIITIS HEEL PAIN:
     Macias DM, Coughlin MJ, Zang K, Stevens FR, Jastifer JR, Doty JF. Low-Level Laser Therapy at 635 nm for Treatment of Chronic Plantar Fasciitis: A Placebo-Controlled, Randomized Study. J Foot Ankle Surg. 2015 Sep-Oct;54(5):768-72. doi: 10.1053/j.jfas.2014.12.014. Epub 2015 Mar 10. PMID: 25769363.

STUDY JUSTIFICATION

The therapeutic and anti-inflammatory effects of red laser light for reducing musculoskeletal pain have been well established, both as a stand-alone therapy and in combination with other wavelengths such as those in the violet and green spectrum. It is hypothesized that pre-treatment with blue low-level laser light may further enhance the cellular environment by supporting mitoNEET function and preserving mitochondrial integrity, in turn enabling the subsequent application of red laser therapy to more effectively stimulate the electron transport chain and restore efficient ATP production, maximizing therapeutic outcomes in musculoskeletal pain relief. Accordingly, it is believed that blue laser pre-treatment, combined

with subsequent standard red laser therapy, will produce pain relief that is comparable to or better than that achieved with red laser therapy alone.

The design of this study is intended to evaluate this hypothesis through assessment of non-inferiority of the efficacy of the combination Erchonia® PPL blue laser light pre-treatment followed sequentially by the standard Erchonia red laser therapy compared with the application of the red laser light therapy alone in providing temporary relief of nociceptive musculoskeletal pain.

To this end, the study design for the current clinical trial is intended to be a replicate of the study design of the clinical trial whose results supported clearance for the following:

- K191257: Simultaneous use of red and violet diode lasers for adjunctive temporary relief of minor chronic neck and shoulder pain of musculoskeletal origin, and
- K212595: FX-405 (red and violet) Laser for adjunctive temporary relief of nociceptive musculoskeletal pain

The indication of '*minor chronic neck and shoulder pain of musculoskeletal origin'* to be evaluated in this clinical study is selected as sufficiently representative of and therefore generalizable to attaining 510(k) clearance for the intended indication for '*adjunctive use in the temporary relief of nociceptive musculoskeletal pain'* for the following two reasons:

1. Clinical data from the prior Erchonia clinical trial evaluating red laser light application to the temporary reduction of neck and shoulder pain of musculoskeletal origin was one of the clinical trial datasets used to support the Erchonia cleared indication for the temporary relief of nociceptive pain, and therefore, the connection between successful treatment for this indication and support of a general indication for treating nociceptive musculoskeletal pain is already established, and

2. Clinical data from a prior Erchonia non-inferiority trial evaluating combined simultaneous treatment with Erchonia violet and red laser light diodes for the temporary reduction of neck and shoulder pain and which used the active arm findings from the study listed in 1. above as the control arm supported clearance for an indication of the Erchonia combined violet and red laser for the temporary reduction of neck and shoulder pain of musculoskeletal origin, and therefore, the design of this study in attaining its goal has already been validated and accepted by the FDA.

STUDY DESIGN

This clinical trial is a single-arm (active treatment only), historical comparative multi-site design intended to demonstrate non-inferiority of the efficacy of pre-treatment with the Erchonia® PPL blue light laser therapy followed sequentially by the standard Erchonia red laser therapy compared with application of the standard Erchonia red laser therapy alone for the temporary relief of nociceptive musculoskeletal pain.

The study design for this clinical trial is a replicate of the study design of the clinical trial whose results supported clearance of K191257 evaluating simultaneous use of red and violet diode lasers for adjunctive temporary relief of minor chronic neck and shoulder pain of musculoskeletal origin, and which was subsequently used to support clearance of K212595 for simultaneous use of red and violet diode lasers for adjunctive temporary relief of nociceptive musculoskeletal pain.

The clinical study that supported clearance of K191257 and K212595 was a single arm (active treatment only), historical comparative design to demonstrate non-inferiority of the standard Erchonia red laser therapy when used in simultaneous combination with violet laser therapy compared with application of the standard Erchonia red laser therapy protocol alone in the temporary reduction of neck and shoulder pain of musculoskeletal origin. The historical comparative active data set for that clinical study used for non-inferiority analysis was the results from the Erchonia® red diode therapy only active subject group attained in the 2001 trial whose results successfully supported 510(k) clearance (K012580) of application of red laser light therapy only for the identical indication. This same historical comparative active data set will be used as the historical comparative Erchonia red laser therapy only active treatment data set for the current proposed clinical study.

SUBJECT GROUP

There will be a single subject group treated in this study. All subjects will receive the active study treatment with the blue laser therapy using the Erchonia® PPL first followed sequentially with the standard Erchonia red laser therapy *(Erchonia XLR8, FDA cleared under K211186)*

Comparative subject data for the red diode alone procedure administration will be taken from the Erchonia 2001 study whose results supported FDA market clearance for K012580.

BLINDING

As all subjects in this study will receive active treatment administrations with the Erchonia® PPL and the Erchonia XLR8, neither subjects nor investigators will be blinded. The statistician analyzing the study results will however be blinded with respect to study success analysis. The data from this combined laser therapy study and the retrospective comparative data from the 2001 red diode only study will be deidentified and presented to the study statistician as ‘Group A’ and ‘Group B’. The statistician will not be aware of which group – A or B – contains the current combined laser therapy data and which contains the retrospective comparative red diode only data.

RANDOMIZATION

As this study is a single treatment group study, randomization to treatment group is not applicable. Therefore, this is a non-randomized trial.

SUBJECTS

Subject Sample
Subjects will be males and females 22 years or older who present with chronic (30 consecutive days or longer) neck and/or shoulder pain diagnosed as being of musculoskeletal origin (osteoarthritis, chronic muscle spasm, cervical and thoracic spine sprain strain) and with a self-reported pain level of 50 or greater on the o to 100 VAS.

Sample Size
There will be 43 qualified subjects enrolled in this study.

Rationale for Sample Size
Sample size is determined to be identical to that of subjects enrolled in the active treatment group that forms the comparative data reference group in this study.

Recruitment
Subjects will be recruited from among:

(i) The Principal Investigator's/test site's pool of existing and new patients
(ii) Referrals from other suitable medical clinics and professionals
(iii) Subjects who respond to the recruitment materials shown in **Appendix A.**

Compensation
A subject will not receive financial or any other form of compensation to participate in this clinical study. However, he or she will also not be charged for the cost of the study treatment with the Erchonia lasers or for the cost of any other directly-related evaluations or measurements that occur as a directly-associated part of his or her participation in the study.

STUDY PROCEDURE

STUDY TEST BATTERY

The following are the study measurement and assessment tools to be used and the variables to be recorded in this clinical study. At each evaluation point, the precise tools and variables that will be employed will be specified.

QUALIFICATION EVALUATION TOOL

PHYSICAL EXAMINATION

(i) Inspection: Manipulation of the neck, shoulders, and cervical spine to evaluate for knots (muscle spasms), tightness, swelling, osteophytes, etc.
(ii) Palpation Assessment: Physical assessment of the bony and soft tissues of the neck, shoulder, and cervical spine through touch with the pads of the fingers, to evaluate for muscle tightness and knotting, trigger points that cause pain and possibly also radiating pain.

BASELINE VARIABLES

NECK/SHOULDER PAIN VARIABLES

(i) Location of pain: right side/left side/back of neck; right/left shoulder
(ii) Duration of pain: months/years since onset of first episode of neck/shoulder pain

CONCOMITANT MEDICATION AND THERAPY USE

(i) Over the counter and prescription medications currently used to relieve neck/shoulder pain, including duration, dosage, and frequency of use
(ii) Non-drug treatments/therapies (conventional, alternative, and experimental) currently used to relieve neck/shoulder pain, including duration and frequency or use/application
(iii) Over the counter and prescription medications currently used, and therapies currently engaged in for any non-pain relief indication, including duration, dosage, and frequency of use

SUBJECT DEMOGRAPHICS: Age, gender, and ethnicity

OUTCOME ASSESSMENT TOOLS

VISUAL ANALOG SCALE (VAS) DEGREE OF PAIN RATING

Subjects will be asked to rate the overall degree of pain experienced in the neck / shoulder region on the following 0-100 mm (0 -10 cm) Visual Analog Pain Scale, by responding to the following question:

“Using the scale below, please mark with a cross (X) a SINGLE SPOT along the 0 to 100 line below that best shows how much **pain you feel in your neck / shoulder** right now. ‘0’ means you feel no pain at all and ‘100’ means you feel the worst pain imaginable. PLEASE MARK ONLY ONE SPOT. DO NOT THINK OF OR WRITE IN A NUMBER.”

The Visual Analog Pain Scale (VAS) is one of the three most commonly used scales for assessing chronic pain. It is a simple scale that consists of a line anchored at one end by a label such as "NO PAIN" and at the other end "WORST POSSIBLE PAIN". The subject marks on the line the spot for the pain intensity, which is then measured.

Standard guidelines for effective use of the VAS that are followed in this clinical study are:

i. The line should be 10, 15 or 20cm long, as other lengths are less reliable.
ii. There should be a small vertical mark at each end, with numbers 0 and 100, and a verbal description.
iii. The verbal description must be in absolute terms (e.g., worst pain imaginable);
iv. The line itself should be clear of any markings and should be horizontal rather than vertical, for more reliable measurements.

Used in the above way, it has been shown that the VAS is a proper ratio scale. Like a thermometer, this means that its two ends are rooted, and a doubling of the score does accurately reflect a doubling of the pain. Consequently, sensitive t-tests and ANOVA methods can be used in the analysis, so that significant differences can be identified with relatively small sample sizes or small differences between groups.
Source: Measuring Pain by Adrian White, Acupuncture in Medicine, November 1998 – Vol 16 No. 2

LINEAR RANGE OF MOTION (ROM) MEASUREMENTS
Mobility in the neck/shoulder region will be measured using a universal inclinometer, as follows:

(i) *Shoulder ROM* will be measured from a seated passive abduction, the relaxed position of parallel to the side of the body through full extension above the head. Maximum movement is 180 degrees.
(ii) *Neck ROM* will be measured in a supine position, from forward position to face over shoulder. Maximum movement is 90 degrees.

SUBJECT SATISFACTION WITH STUDY OUTCOME
The subject is asked to rate how satisfied he or she is with any change in neck/shoulder pain following completion of the laser administration procedure with the Erchonia Lasers 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 pain in your neck and/or shoulder following the study treatment with the study laser devices?”

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

STUDY PROCEDURE PROTOCOL

PRE-TREATMENT ACTIVITIES

Pre-treatment activities will be performed at the study site prior to administering the sequential Erchonia® PPL blue laser therapy followed by the standard Erchonia XLR8 red laser therapy.

STUDY QUALIFICATION

SIGNING OF INFORMED CONSENT FORM

The PI 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 IDENTIFICATION NUMBER

The subject is assigned a unique de-identified subject identification number based upon his or her order of entry into the study. The Subject ID number will comprise the initials of the test site Principal Investigator's first and last name followed by a single digit number that represents the test site number (e.g. test site #1 = 0, test site #2 = 1, etc.) and then a two-digit number that represents the subject's order of entry in the study.

For example, the 14th subject to be enrolled at test site #2 with Principal Investigator John Black will have a Subject ID of JB114.

STUDY QUALIFICATION EVALUATION: INCLUSION/EXCLUSION CRITERIA

INCLUSION CRITERIA

To be eligible for study participation, a subject must satisfy each of the following criteria.

1. Signed informed consent form
2. 22 years of age or older
3. Primary language is English
4. Subject presents with one or more of:

   - chronic neck pain on the right side of the neck and/or the left side of the neck and/or the back of the neck; and/or
   - chronic shoulder pain on the right shoulder and/or the left shoulder.

5. Subject is diagnosed with of one or more of the following:

   - Osteoarthritis: Degenerative Joint Disorder (DJD)
   - Chronic Muscle Spasms
   - Cervical and Thoracic Spine Sprain Strain

   … based on the following criteria specific to each condition:

   - Patient History
   - Medication Use History
   - Records Review: where available, such as x-ray, MRI, and CAT scan reports

- Physical Examination

Specific criteria to diagnose each condition are as follows:

A. Osteoarthritis: Degenerative Joint Disorder (DJD)
   - Patient History: Previous trauma or infection to the area.
   - Medication Use History: Anti-inflammatory medications; either over the counter (e.g., Advil, Motrin, Aspirin); prescription medications (e.g., Celebrex, Vioxx)
   - Previous Records Review: DJD indicated.
   - Physical Examination: Pain and pain with ROM evaluation; reduced ROM, particularly passive ROM motion; cracking/popping/creaking sound upon movement (ROM); possible joint swelling; possible bone spurs (osteophytes).

B. Chronic Muscle Spasms
   - Patient History: Previous trauma; "frozen" shoulder and/or neck; history of restricted range of motion; pain relief through heat application and/or physical manipulations such as massage and physical therapy.
   - Medication Use History: Over the counter/prescription muscle relaxers and palliatives.
   - Previous Records Review: Lack of DJD indicated.
   - Physical Examination: Limited ROM; muscle tightness/knotting; tenderness and pain upon palpation; possible radiation pain upon palpation of tender spots (trigger points).

C. Cervical and Thoracic Spine Sprain Strain
   - Patient History: Injury or pain initiated after motion or repetitive motion and exacerbated by motion; history of an old injury that can be exasperated acutely; pain and weakness on flexion; increased joint pain at the end range of motion.
   - Medication Use History: OTC and/or prescription muscle relaxants or anti-inflammatory medications.
   - Previous Records Review: Muscle or ligament injury indicated.
   - Physical Examination: Pain that worsens with movement (active and/or passive ROM); reduced ROM; muscle weakness; stiffness; tenderness upon palpation; possible swelling.

6. Pain is chronic: symptoms have persisted for longer than the past 30 days
7. Subject's self-reported Degree of Pain rating on the 0-100 VAS pain scale is 50 or greater.
8. Subject is willing and able to refrain from consuming any over the counter and/or prescription medication(s) and/or herbal supplements intended for the relief of pain and/or inflammation, including muscle relaxants throughout the course of study participation
9. Subject is willing and able to refrain from engaging in any non-study procedure therapies for the management of his or her neck/shoulder pain throughout the course of study participation, including conventional therapies such as physical therapy, occupational therapy and hot or cold packs, as well as alternative therapies such as chiropractic care and acupuncture

EXCLUSION CRITERIA

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

1. Presenting primary pain is located outside or in addition to the region of the neck (right side/left side/back) or the shoulder (right and/or left side)
2. Etiology of neck/shoulder pain cannot be definitively diagnosed; or has been diagnosed as being in whole or in part other than that of osteoarthritis, chronic muscle spasms or cervical and thoracic spine sprain strain; or other potentially contributing etiologies cannot be satisfactorily ruled out
3. Pain is acute: symptoms prevailed for fewer than each of the prior 30 days
4. Current active chronic pain disease: such as chronic fatigue syndrome and fibromyalgia
5. Use of analgesics or muscle relaxants within 7 days prior to study procedure administration
6. Use of systemic corticosteroid therapy (inhaled and topical corticosteroids permitted), narcotics or Botulinum toxin (Botox®) injection in the neck / shoulder region within 30 days prior to study procedure administration
7. Active cancer or treatment for cancer within the last 6 months
8. Unstable cardiac disease, such as recent cardiac arrhythmia, congestive heart failure or myocardial infarction
9. Prior surgery to the neck/shoulder region
10. Known herniated disc injury
11. Active infection, wound or other external trauma to the areas to be treated with the laser
12. Medical, physical, or other contraindications for or sensitivity to light therapy
13. Serious known mental health illness such as dementia or schizophrenia; psychiatric hospitalization in the past two years
14. Pregnant or breast feeding
15. Participation in a research study within the past 30 days

PRE-TREATMENT EVALUATIONS

The pre-treatment evaluation phase directly follows successful study qualification, on the same day.

BASELINE VARIABLES

- Neck / Shoulder Pain Variables
- Concomitant Medication and Therapy Use
- Subject Demographics

OUTCOME ASSESSMENTS

- Visual Analog Scale (VAS) Degree of Pain Rating
- Linear Range of Motion (ROM)

TREATMENT ADMINISTRATION PHASE

TREATMENT ADMINISTRATION PROTOCOL

- The treatment administration phase of the study directly follows successful completion of the pre-treatment evaluation phase, on the same day.
- The treatment administration phase comprises a single sequential treatment administration session with the Erchonia® PPL blue laser therapy followed by the standard Erchonia red laser therapy using the Erchonia XLR8.
- The total treatment administration time is eighteen (18) minutes.
- The treatment is administered at the test site.
- The subject enters the treatment room, is seated comfortably, and correctly fitted with the protective eyewear.

The treatment administration protocol is as follows:

(i) Erchonia PPL blue laser therapy treatment administration protocol:

The single treatment administration protocol commences with the blue laser therapy treatment protocol using the Erchonia PPL and is as follows:

1. The Erchonia® PPL device is positioned approximately 2 to 3 inches from the initial targeted treatment area of the left shoulder, then activated.
2. The pulsed PPL laser treatment is administered by using a slow sweeping motion beginning at the left shoulder, moving across the cervical spine, and continuing to the right shoulder maintaining the distance from the skin surface of approximately 2 to 3 inches throughout the process.
3. This motion is then reversed, sweeping from the right shoulder back across the cervical spine to the left shoulder, again maintaining the distance from the skin surface of approximately 2 to 3 inches throughout the process.
4. This bidirectional sweeping technique is continuously performed until the device turns off which is a total duration of five (5) minutes.

(ii) Erchonia XLR8 standard red laser therapy treatment administration protocol:

Immediately following completion of the treatment administration with the Erchonia PPL blue laser therapy, the treatment administration with the standard Erchonia XLR8 red laser therapy commences. The red laser therapy treatment administration protocol is identical to that in the retrospective comparative control study, and is as follows:

1. The Erchonia® XLR8 is positioned and centered 6 inches above the subject's sagittal suture (top of the head), then activated.
2. One minute of pulsed laser is applied to the sagittal suture (top of the head)
3. The next treatment area is the left cervical, shoulder and torso area. The laser is applied starting in the cerebral region, at the top of the ear, lasering the left cervical anterior and posterior muscles, then working the laser down over the left shoulder and torso anterior and posterior muscles, maintaining the laser 6 inches from the skin. This part of the treatment takes two (2) minutes.

4. Step 3 is repeated to the subject's right cervical, shoulder and torso area for 2 minutes.

5. One minute of pulsed laser is then applied to right shoulder during passive external rotation of the shoulder. The anterior muscles of the right shoulder (pectoralis group) are lasered, with the subject's arm bent at the elbow.
6. One minute of pulsed laser is then applied to the right shoulder during passive adduction of the subject's right arm and shoulder. The posterior muscles of the right shoulder are lasered.
7. One minute of pulsed laser is then applied to the right cervical muscle and trapezius muscle during passive left lateral flexion of the cervical spine. Starting in the neutral position of the head, the laser light is applied to the right cervical muscles and right trapezius muscles.
8. One minute of pulsed laser is then applied to the right sternocleidomastoid and scalene muscles during passive range of motion. The laser light is applied to the right sternocleidomastoid and scalenus muscles.
9. Step 5 is then repeated to the left shoulder.
10. Step 6 is then repeated to the left shoulder.
11. Step 7 is then repeated to the left cervical spine.
12. Step 8 is then repeated to the left sternocleidomastoid and scalenus muscles.

13. The subject's protective eyewear is removed, and the single treatment administration session is over.

JUSTIFICATION FOR THE TREATMENT ADMINISTRATION PROTOCOL

The treatment administration protocol with the red laser device in this current study is identical to that which was evaluated in the comparative retrospective study to enable direct comparison of findings between the two studies and statistical analysis of different group outcomes. The only modification in the current study is the addition of a 5-minute treatment with the Erchonia PPL laser, administered immediately prior to the red laser therapy which is the treatment arm being evaluated for non-inferiority.

TREATMENT ADMINISTRATION PHASE EVALUATIONS: STUDY ENDPOINT

Within three (3) minutes of completion of the procedure administration phase, study endpoint evaluation will occur.

OUTCOME ASSESSMENTS

- Visual Analog Scale (VAS) Degree of Pain Rating
- Linear Range of Motion (ROM)
- Subject Satisfaction with Study Outcome Rating
- Adverse Events Evaluation

POST-TREATMENT ACTIVITIES

The post-treatment evaluation phase of this study will commence immediately following completion of the treatment administration phase evaluations and will last for two (2) days (48 hours).

The post-treatment outcome assessments will be recorded by the subject in his or her own home on forms provided by the test site. The subject will be instructed on when and how to complete the forms and how to return them to the test site prior to leaving the test site on the treatment administration day.

24 HOURS AND 48 HOURS POST-TREATMENT EVALUATIONS

The subject will be required to record the following at home on the forms provided by the test site at 24 hours and again at 48 hours after completion of the treatment administration phase at the test site.

OUTCOME ASSESSMENTS

- Visual Analog Scale (VAS) Degree of Pain Rating
- Linear Range of Motion (ROM)
- Subject Satisfaction with Study Outcome Rating
- Adverse Events Evaluation

STATISTICAL ANALYSIS PLAN

Populations Examined

Two (2) subject populations will be analyzed, as applicable:

(i) **Intent-to-Treat (ITT) Population:** All enrolled subjects regardless of whether any measures are recorded and/or treatment is administered.

(ii) **Per-Protocol (PP) Population**: All enrolled subjects who completed the study per protocol through to the 48-hour post-treatment evaluation, excluding subjects with major protocol deviations, incompletes, etc.

Primary analysis of efficacy will be according to the intent to treat (ITT) population and the secondary supportive analysis will be according to the per protocol (PP) population. Non-inferiority will be established if both the ITT and PP analyses agree.

Handling of Missing Data

Missing data will be handled through multiple imputation analysis, a strategy to handle missing values in a clinical trial wherein each missing value is replaced with a set of plausible values that represent the uncertainty about the right value to impute. The exact method of multiple imputation analysis will be determined after study completion depending on factors such as the amount of missing data and whether it is determined that the data are missing at random (MAR) or missing not at random (MNAR).

PRIMARY EFFICACY OUTCOME MEASURE: CHANGE IN SUBJECT SELF-REPORTED VAS PAIN RATING FROM BASELINE TO STUDY ENDPOINT

The aim of this study is to determine if the treatment effect of the sequential therapy with the Erchonia® PPL blue laser therapy followed by the Erchonia® XLR8 standard red laser therapy for the active treatment group in this study is equal to or superior to that attained for the active comparative treatment group in the comparative reference study who received the standard red laser therapy alone.

Proportion of Successes

The primary efficacy outcome measure for this clinical study is identical to that of the comparative reference study and is defined as the change in subject self-reported Visual Analog Scale (VAS) pain rating from baseline to study endpoint evaluation, with study endpoint defined as within 3 minutes of completion of the study single sequential treatment administration with the Erchonia® PPL blue laser therapy followed by the standard Erchonia red laser therapy administered using the Erchonia® XLR8.

Individual Subject Success Criteria
individual subject success criteria is defined as a 30% or greater decrease in self-reported neck and shoulder pain rating on the 0-100 VAS at study endpoint relative to baseline.

Overall Study Success Criteria.
Overall study success criteria is defined as at least 65%±5% of subjects in the current study meeting the study individual subject success criteria.

Justification for Study Success Criteria

The clinical relevance and justification of the individual and overall study success criteria is as follows:

- This study is a non-inferiority study, such that the research hypothesis is that the sequential combination therapy with the Erchonia® PPL blue laser and the standard Erchonia red laser therapy is either equivalent to or superior to the standard Erchonia red diode only therapy in effecting a clinically meaningful reduction in neck and shoulder pain of musculoskeletal origin, based upon the data attained from the red diode only clinical trial conducted in 2001 whose results successfully supported 510(k) clearance of application of the PL3000 red diode only for the identical indication being sought through the results of this clinical trial.
- The individual subject success criteria in this clinical study is identical to that of the comparative reference study.
- The overall study success criteria in this clinical study is based on the actual proportion of individual subject successes attained during the comparative reference trial for the active red diode treatment group, of 65%. The ±5% is the selected equivalence margin (δ), the maximally clinically acceptable difference for which the range of values (60% to 70%) for which the efficacies are “close enough” to be considered equivalent.
- Non-inferiority will be established if the proportion of subjects who attain the individual subject success criteria is no more than 5% less than the reference subject group (i.e. no less than 60%).

Hypotheses

- *Null Hypothesis*: Sequential treatment application of the Erchonia® PPL blue laser therapy followed by the standard Erchonia® red laser therapy using the XLR8 is inferior to treatment application of the Erchonia red laser therapy alone in reducing neck and shoulder nociceptive pain of musculoskeletal origin to the effect of 60% or fewer subjects attaining a 30% or greater reduction in neck and shoulder pain at study endpoint evaluation relative to baseline.

  $H_0 : P \leq 60\%$; *where P = individual subject responder rate*

- *Alternative Hypotheses*: Sequential treatment application of the Erchonia® PPL blue laser therapy followed by the standard Erchonia® red laser therapy using the XLR8 is NOT inferior to (i.e., is equivalent to or superior to) treatment application of the Erchonia red laser therapy only in reducing neck and shoulder nociceptive pain of musculoskeletal origin to the effect of greater than 60% of subjects attaining a 30% or greater reduction in neck and shoulder pain at study endpoint evaluation relative to baseline.

  $H_1 : P > 60\%$; *where P = individual subject responder rate*

Evaluation Time Point

Study endpoint evaluation was preestablished as occurring immediately (within 3 minutes) following completion of administration of the second component of the sequential study treatment with the standard Erchonia® red light laser device. Study primary success analysis is preestablished at study endpoint relative to baseline, identically to that in the 2001 reference comparative study.

Change Scores

- T-test analysis of the difference in the mean change in VAS levels from baseline to endpoint between the dual-diode and red only diode treatment administration groups. Significance levels will be considered at the $p<0.05$ level.

- A t-test for two independent sample will be performed to evaluate the significance of the difference in the mean change in VAS pain scores from baseline to endpoint evaluation between the two study groups to evaluate for equivalency to support the support the conclusion of the proportion of successes evaluation. Significance levels will be considered at the $p<0.05$ level.

SECONDARY EVALUATIONS

The following secondary evaluations will be performed on the per protocol study data set only. As no claims are intended to be made based on secondary measures, the findings will be presented through descriptive analysis and qualitative trending only, without evaluation for or claims of statistical significance.

- Change in mean neck and shoulder pain VAS ratings across study duration: baseline, endpoint, 24 hours, and 48 hours post-procedure.
- Change in linear ROM measurements at study endpoint relative to baseline.
- Subject satisfaction with study outcome ratings across study duration.

INDIVIDUAL TEST SITES

Results will be presented by individual test site for comparison.

INDIVIDUAL SUBJECT RESULTS

Individual subject results for the primary study outcome measure will also be presented.

SAFETY ANALYSIS

Safety analysis will be based on all enrolled subjects and will be assessed by evaluating and comparing the frequency and incidence of observed and/or reported adverse events between subjects enrolled in the current study and subjects enrolled in the comparative reference study. A chi-square test with a continuity correction will be performed to compare the percentage of subjects who had adverse events between the two subject groups.

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 evaluating application of Erchonia low level laser light, including numerous evaluating Erchonia lasers for the treatment of various pain conditions, including neck and shoulder nociceptive pain of musculoskeletal origin, have not typically yielded any adverse events or reactions.

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® PPL 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 B.**

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 C.**

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