ERCHONIA® EVRL OTC™

A Pilot Evaluation of the effect of the Erchonia® EVRL OTC™ for the relief of diabetic peripheral neuropathy foot pain

ERCHONIA CORPORATION

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PURPOSE OF STUDY
The purpose of this pilot study is to determine the effectiveness of the Erchonia® EVRL OTC™, manufactured by Erchonia Corporation (the Company), in providing Over the Counter use for temporary relief of chronic foot pain arising from diabetic peripheral neuropathy (DPN) in adults 18 years and older that have been previously diagnosed with DPN by a qualified physician.

STUDY DURATION
The estimated total duration of the study is about two months.

EXPECTED RESULTS
Following completion of the study procedure administration protocol with the Erchonia® EVRL OTC™, it is anticipated that compared with baseline, subjects will show a reduction in chronic foot pain at study endpoint evaluation.

RESOURCES
This clinical study protocol design and content is based on the clinical study protocols whose implementation outcome was used to successfully support FDA clearances to market the Erchonia® 635nm red diode and 405nm violet diode low level lasers for the following pain reduction related indications:

1. **K180197:** *Erchonia® FX-635:* is indicated for the following two indications:
   a. as an adjunct to provide relief of minor chronic low back pain of musculoskeletal origin.
   b. as an adjunct to reducing chronic heel pain arising from plantar fasciitis.
2. **K132940:** *Erchonia® Allay™:* is indicated as an adjunct to reducing chronic heel pain arising from plantar fasciitis.
3. **K072206:** *Erchonia® EML Laser:* is indicated for the temporary reduction in post-surgery pain at 24 hours after surgery following bilateral breast augmentation surgery.
4. **K041139:** *Erchonia® EML Laser*: is indicated as an adjunct to liposuction procedures of the thighs, hips and stomach for reduction of pain associated with the recovery process.
5. **K012580:** *Erchonia PL2000*: is indicated for adjunctive use in providing temporary relief of minor chronic neck and shoulder pain of musculoskeletal origin.
6. **K191257:** *Erchonia® EVRL:* is indicated 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.

In addition, a previous Erchonia laser emitting 635-640nm line generated laser, received FDA Over The Counter (OTC) indications based on data from a lay person (non-doctor) usability and efficacy trial under 510(k) # **K162578 and K143007.**

DEVICE DESCRIPTION

Performance Characteristics

The Erchonia® EVRL OTC™ Laser will be self-administered by the subject at home. Each EVRL OTC™ administration will last 5 minutes per foot, for a total treatment time of 10 minutes.

The Erchonia EVRL OTC™ Laser is a hand-held single diode, variable hertz laser that is portable, self-contained, lightweight, and battery operated.

The Erchonia® EVRL OTC™ (Model# EVRL) is a low-level laser system that uses two semi-conductor diodes; visible red light: 630-650 nm (7.5mW ± 1mW) and visible violet light: 380-450 nm (<5mW). The Erchonia® EVRL OTC™ (Model# EVRL) is a variable hertz device. The variable hertz feature of the Erchonia® EVRL OTC™ (Model# EVRL) is a pulsed wave, defined as containing a selected series of breaks, variances.

The Erchonia® EVRL has been classified by the FDA as a Class II device and a Class 2 laser in accordance to IEC 60825-1 (complies with 21 CFR 1040.10 and 21 CFR 1040.11 by Laser Notice #50). The performance parameters and intended use of the Erchonia® EVRL laser is compliant to the internationally recognized safety testing standards for medical devices. The testing of the Erchonia® EVRL laser device includes functional performance, electrical, safety and component verification, in accordance with the FDA QS requirement, validated annually through ISO 13485 audits. The software incorporated into the operation of the Erchonia® EVRL laser complies with FDA and ISO Software Development and Validation regulations.

The components of the device include a separate inductive charging base powered by an external class II medical power supply which runs on AC power of 120 Volt 60 Hz or 220 Volt 50 Hz by plugging to main power. An internal, rechargeable, battery which powers the two semi-conductor diodes. A touchscreen communicates with the PCB to initiate, stop or pause the energy flow to the laser diodes. The laser diodes can only be on or off; there is no user interface that allows the end user to alter the laser diode output. The treatment protocol is factory set and cannot be altered by the end user.

The device contains software that is loaded into the 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. The exterior material of the Erchonia® EVRL is 60601-TG AL with powder coating and anodizing finish. The separate inductive charging base is wonderloy PC-510 which is Polycarbonite+ABS blend & is flame retardant.

The associated accessories include:

- (1) Inductive charging base with power supply

- (1) Patient protective eyewear (sufficiently and effectively block the laser light spectrum at OD 2+ @ 635nm, OD 0.75 @ 405nm VLT60)

Fig. 1

1. Power Button (ON/OFF)
2. Laser ON Light
3. Power ON Light
4. Touch Screen
5. Pivoting Laser Mount
6. Laser Diodes
7. Covered Micro USB (For Manufacturer Use Only)

CHARGER BASE

Directions to set Device on Charger Base

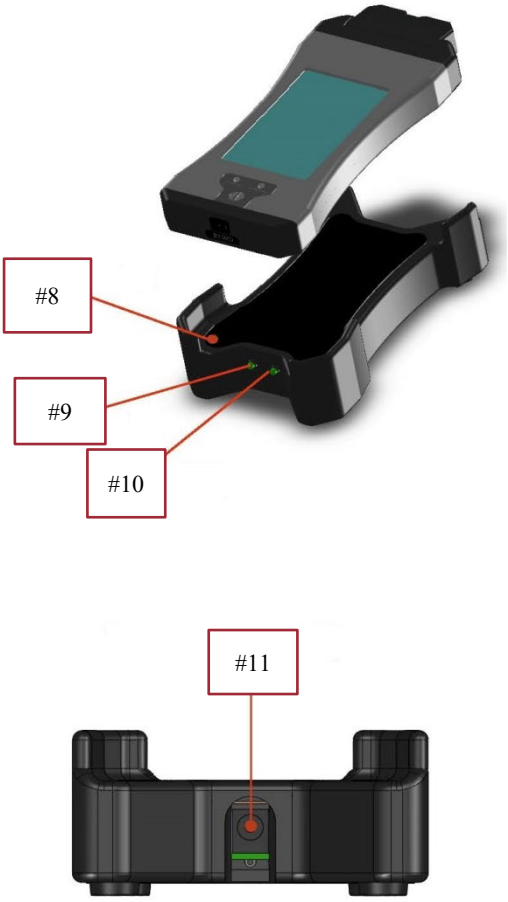


Fig. 2

POWER SUPPLY

Fig. 3

8. Inductive Charger Base
9. Charger Base Power Light
10. Docked Light
11. Charger Base Connector Port
12. Power Supply Connector
13. Detachable Power Supply Cord

Physical Characteristics

Weight: Laser - .95lbs / .42kgs. Charger Base - .55lbs / .25kgs

(Height x Depth x Width)
Size: (Laser) 6.9” x 3.10” x .76”/ 17.52cm x 7.87cm x 1.93cm
Size: **(Charging Base)** 5.7” x 3.5” x 1.65”/ 14.47cm x 8.88cm x 4.19cm

Device

- Full color touch screen control center
- Exterior Materials: 60601-TG AL
- Finishing: Powder Coating and Anodizing Finish

Laser

- Qty: 2, Class 2 line generating diode modules
- Output: (Red) .5mW ±1.00mW
- Output: (Violet) 405 nm <5mW
- Wavelength: Red 640 nm± 10nm
- Wavelength: Violet 405nm± 10nm
- Modulation: Constant Wave- 50% Duty Cycle

Power

- Source: 100-240Vac, 50-60Hz, 0.5A; 12Vdc 1.5A

Temperature

- Operating Temp: 59 to 85°F (15 to 29°C), Relative Humidly: <50%
- Transporting: 14 to 140°F (-10 to 60°C) Relative Humidly: <95%

POWER BUTTON (ON/OFF) [1]

The Power Button allows you to turn the device ON "|" or OFF "O". To turn the device ON, press and Hold this button, (approximately 4 seconds) until the green (#3 Power On Light) turns on. To turn off the device it is recommended to use the **"Power Down"** icon method, explained in the **Operation** section of this manual**.** In the unlikely event that your device stops responding to touches, by pressing and holding the power button for 15 seconds will force shut down the device. This is only recommended if the device cannot be turned off from the **"Power Down"** screen method.

LASERS ON LIGHT [2]

The "Lasers On" light is an LED indicator that will light up when the Lasers are ON and shut off when the lasers are OFF

POWER ON LIGHT [3]

The "Power On" light is an LED indicator that will display a constant green light when the device is powered on and shut off only when the device is OFF.

TOUCH SCREEN [4]

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.

PIVOTING LASER MOUNT [5]

The Pivoting Laser Mount allows you to adjust the laser angle (up to 20º each direction) based on your preference.

LASER DIODES [6]

The device consists of two electronic laser diodes, with patented optics. These laser diodes when activated by the internal power source generate laser energy thereby emitting on one side a red beam and the other side a violet beam. This is a specially designed and patented device created to ensure the laser beam is focused and directed for the most optimal use. The device can be programed with up to 4 defined Hz

frequencies (two for each diode).

INDUCTIVE CHARGER BASE [8]
The Inductive Charger Base is a custom based system specifically designed to charge the laser device. It is an inductive charging system that charges the device wirelessly. The Charger Base must be connected to the power supply and the power supply must be plugged into a wall socket for Charger Base to receive power. Once powered up, the Laser device is placed on Charger Base with the touch screen facing up and Laser diodes facing away from Charger Base LED lights.
NOTE: The lasers do NOT operate when the handheld device is in the charger base

CHARGER BASE POWER LIGHT [9]
The Charger Base "Power" Light is the power indicator LED that will light up when the energized Power Supply connector is plugged into the Inductive Charger Base.

DOCKED LIGHT [10]
The "Docked" light is an indicator LED that will light up to indicate the device is correctly docked in the inductive charger base. The LED will flash ON and OFF when correctly in place and turn off when removed from the inductive charger base.
NOTE: If the Laser device is incorrectly placed in the inductive charger base the LED will **not** turn on and the battery will **not** re-charge.

CHARGER BASE CONNECTOR PORT [11]
The Charger Base Connector Port is the location to plug the [#11] Power Supply Connector in to supply power to the inductive charger base.
NOTE: Make sure the Power Supply Connector is plugged into the inductive Charger Base at this location prior to plugging Power Supply into a wall socket.

POWER SUPPLY CONNECTOR [12]
The Power Supply Connector plugs into the Inductive Charger Base Connector Port to provide power to charger base. The Power Supply comes with a Cord (#13) that must be plugged into Power Supply and wall socket in order to charge.

This device should be operated in temperatures between 59 to 85°F (15 to 29°C) <50% relative humidity and transported in temperatures between 14 to 140°F (-10 to 60°C) relative humidity <95%.

NOTE: It is recommended that the Power Supply Connector is plugged into the Charger Base at this location prior to plugging Power Supply into a wall socket.
NOTE: #13 detachable Power supply cord is mains isolation, in an emergency unplug from electric receptacle.

PROTECTIVE EYEWEAR

The Erchonia® is classified by the FDA/IEC as a Class 2 laser device. This designation represents a current standard for use in order to ensure the safety of the user. 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 user during treatment.

Characterization of all Accessories
The accessories to the device are:

- Inductive Charging Base
  Input: 1.5A 12V

Fig. 4

- Power Supply
  100-240Vac, 50-60Hz, 0.5A;
  12Vdc 1.5A
  IEC 60601-1 Third edition including amendment 1
  CE/CB Standards compliant

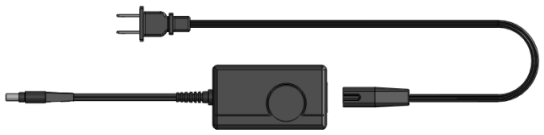


Fig. 5

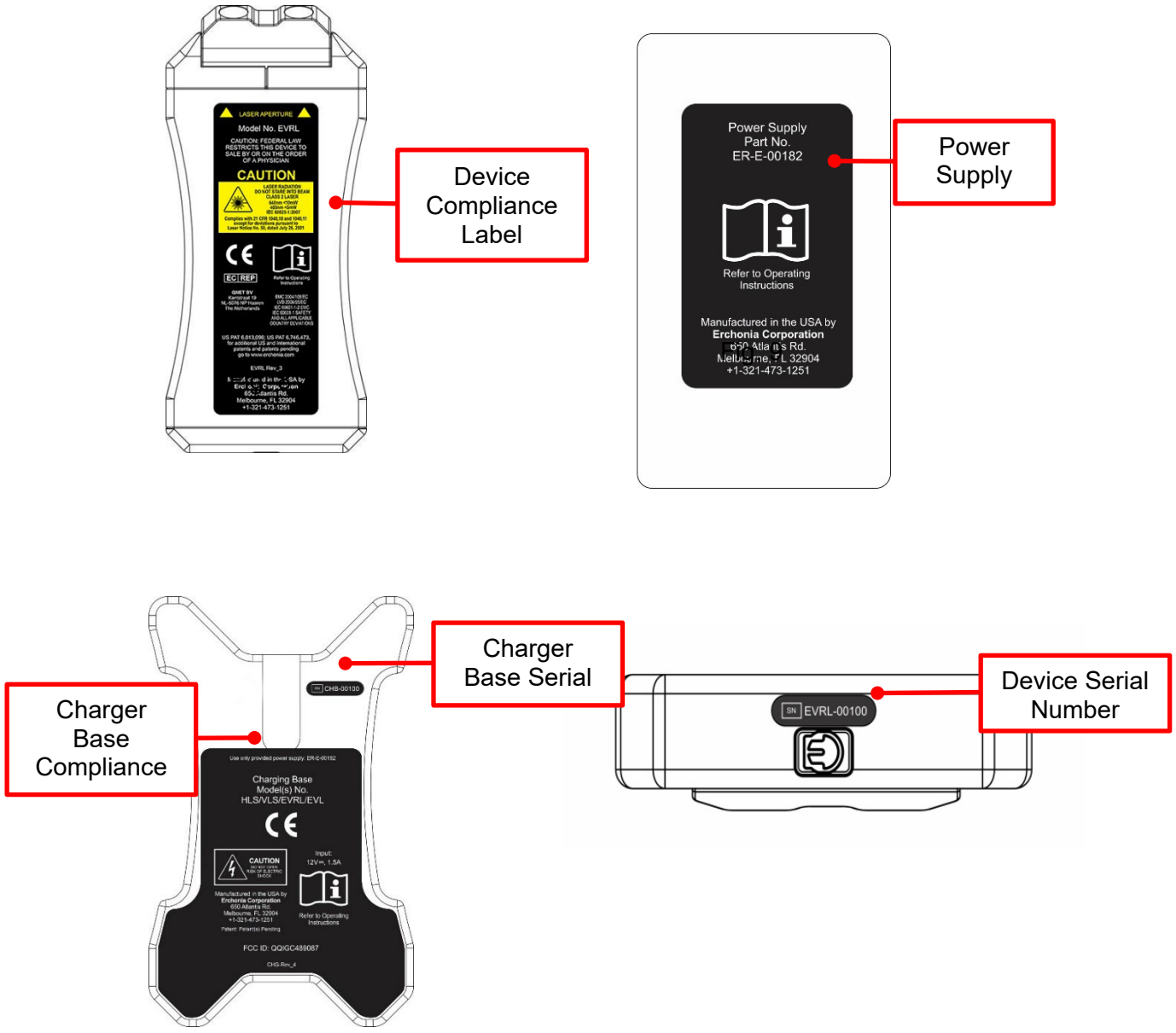
- The safety glasses, sufficiently and effectively block the laser light spectrum at OD 2+ @ 635nm, OD 0.75 @ 405nm VLT60.
  Height: 40 mm
  Width: 145 mm
  Length: 165 mm

Fig. 6

Labeling

The Erchonia EVRL OTC Laser is manufactured in accordance to the Good Manufacturing Procedures consistent with national regulatory agencies; such as FDA, EU, HC, TGA, and Anvisa. Per ISO and FDA standards the device and laser are classified as Class II.

Each of these governing agencies requires specific labeling. All required labels are affixed according to the relevant codes, as shown in Figure 3 below.



FOOD AND DRUG ADMINISTRATION (FDA) DETERMINATION OF NON-SIGNIFICANT RISK (NSR) STATUS

(i) Regulatory Clearances**:** The Food and Drug Administration (FDA) has determined the family of Erchonia® low level laser 635 red diode and 405 violet diode devices to be non-significant risk (NSR) through numerous **510(k) clearances**, as follows.

1. **K191257:** *Erchonia® EVRL:* is indicated 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.

2. **K180197:** *Erchonia® FX-635™ Laser*: is indicated for the following two indications:

   a. as an adjunct to provide relief of minor chronic low back pain of musculoskeletal origin.
   b. as an adjunct to reducing chronic heel pain arising from plantar fasciitis.

2. K132940: *Erchonia® Allay™:* is indicated as an adjunct to reducing chronic heel pain arising from plantar fasciitis.

3. K072206: *Erchonia® EML Laser:* is indicated for the temporary reduction in post-surgery pain at 24 hours after surgery following bilateral breast augmentation surgery.

4. K050672: *Erchonia® EVRL Laser*: The Erchonia EVRL Laser is generally indicated:

   a. while using the red diode, for adjunctive use in providing temporary relief of minor chronic neck and shoulder pain of musculoskeletal origin, and
   b. while using the blue diode, to treat dermatological conditions, and specifically indicated to treat moderate inflammatory Acne Vulgaris.

5. K041139: *Erchonia® EML Laser*: is indicated as an adjunct to liposuction procedures of the thighs, hips and stomach for reduction of pain associated with the recovery process.

6. K100509 & K130741: *Erchonia® THL1 Laser & Erchonia® PL5000*: is indicated for adjunctive use in providing temporary relief of minor chronic neck and shoulder pain of musculoskeletal origin.

7. K130996: *Erchonia® XLR8™*: The Erchonia XLR8™ is indicated for the following three indications:

   a. adjunctive use in providing temporary relief of minor chronic neck and shoulder pain of musculoskeletal origin
   b. as an adjunct to liposuction procedures of the thighs, hips and stomach for reduction of pain associated with the recovery process
   c. temporary reduction in post-surgery pain at 24 hours after surgery following bilateral breast augmentation surgery

8. K123237 & K133718: *Erchonia® Zerona™ 2.0 Laser & Zerona®-Z6*: 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.

9. **K121695 & K082609:** *Erchonia® ML Scanner (MLS) & Erchonia® Zerona:* 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.

10. **K21690 & K120257:** *Erchonia® MLS, Zerona, Zerona-AD*: 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 the upper arms.

11. **K082609:** *Erchonia® ML Scanner (MLS)*: is indicated for use as a non-invasive dermatological aesthetic treatment for the reduction of circumference of hips, waist and thighs.

(ii) Pre-IDE Reviews**:** FDA has previously reviewed numerous clinical study protocols employing various Erchonia® Corporation 635 nm red diode and the 405 nm violet diode low level laser devices, including each of the clinical studies conducted in support of the above 510(k). For each of the FDA's pre-IDE reviews of Erchonia 635 nm red diode and the 405 nm violet diode low level laser clinical study protocols, there was concurrence from FDA that the clinical study protocols and application of the Erchonia laser devices therein were considered non-significant risk (NSR).

INSTITUTIONAL REVIEW BOARD (IRB) DETERMINATION OF NON-SIGNIFICANT RISK (NSR) STATUS

Erchonia® Corporation 635 nm red diode and 405nm violet diode low level laser devices have been determined to be non-significant risk (NSR) when applied in various clinical studies through several IRBs, as follows:

- Western Institutional Review Board (WIRB®) has previously determined Erchonia low level laser devices to be non-significant risk (NSR) when applied in the following clinical studies:

  1. **WIRB PRO NUM: 20131165:** An Evaluation of the Effect of the Erchonia EVRL on Neck and Shoulder Pain

  2. **WIRB PRO NUM: 20131165:** Erchonia® ZERONA 6 Headed Scanner (EZ6): An evaluation of the effect of the Erchonia® ZERONA 6 Headed Scanner (EZ6) six-week treatment protocol on circumference reduction of the waist, hips, highs and upper abdomen clinical study

  3. **WIRB PRO NUM: 20130851:** Erchonia® ML Scanner (MLS): An evaluation of the effect of the Erchonia® ML Scanner (MLS) laser on increasing blood circulation in individuals with chronic heel pain clinical study

  4. **WIRB PRO NUM: 20130488:** Erchonia® TMJ laser: A pilot evaluation of the effect of the Erchonia® TMJ Laser on reducing jaw pain and improving jaw function for individuals with temporomandibular joint (TMJ) disorder

5. **WIRB PRO NUM: 20121548:** Erchonia® MLS: A double-blind, placebo-controlled randomized evaluation of the effect of the Erchonia® ML Scanner (MLS) laser on reducing pain associated with degenerative arthritis (osteoarthritis) of the midfoot clinical study protocol

6. **WIRB PRO NUM: 20120787:** Erchonia® MLS: A double-blind, placebo-controlled randomized evaluation of the effect of the Erchonia® ML Scanner (MLS) on low back pain clinical study protocol

7. **WIRB PRO NUM: 20111793:** Erchonia® MLS: A double-blind, placebo-controlled randomized evaluation of the effect of the Erchonia® ML Scanner (MLS) laser on chronic heel pain clinical study protocol

8. **WIRB PRO NUM: 20110331:** Erchonia® MLS: An evaluation of the effectiveness of the Erchonia® ML Scanner (MLS) as a non-invasive dermatological aesthetic treatment for the reduction of circumference of the upper arms clinical study protocol

9. **WIRB PRO NUM: 20120911:** Erchonia® MLS: A double-blind, placebo-controlled randomized evaluation of the effect of the Erchonia® ML Scanner (MLS) on body contouring of the waist, hips and thighs five-day treatment protocol clinical study protocol

10. **WIRB PRO NUM: 20110758**: Erchonia® MLS: A pilot evaluation of the effect of the Erchonia® ML Scanner (MLS) laser device on enhancing body weight loss, fat loss and circumference reduction of the waist, hips and thighs clinical study protocol

11. **WIRB PRO NUM: 20121330:** Erchonia LUNULA™**:** An Evaluation of the Effect of the Erchonia LUNULA™ on Treating Toenail Onychomycosis Clinical Study Protocol; Version 6.0 August 7, 2012

12. **WIRB PRO NUM: 20110461:** Erchonia FX-405™**:** An Evaluation of the Effect of the Erchonia FX-405™ on Treating Toenail Onychomycosis Clinical Study Protocol; Version 3.0 March 19, 2011

13. **WIRB PRO NUM: 20120489:** Erchonia® MLS: A double-blind, placebo-controlled randomized evaluation of the effect of the Erchonia® ML Scanner (MLS) on lipid panel levels clinical study protocol

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.

STUDY INDICATION, THEORY OF MECHANISM OF OPERATION, STUDY RATIONALE & SUPPORTING MATERIALS

STUDY INDICATION: CHRONIC PAINFUL DIABETIC PERIPHERAL NEUROPATHY

The study indication to be evaluated in this study is the relief of chronic foot pain arising from diabetic peripheral neuropathy.

STATISTICS

Peripheral neuropathy is one of the most common chronic diseases and a leading cause of adult disability in the U.S. Of the over 100 known types of neuropathy, diabetic neuropathy represents over a third of all neuropathies, making diabetes the leading cause of peripheral neuropathy. Due to the increasing prevalence of diabetes, there are now about 15-18 million Americans with diabetic peripheral neuropathy, about 60% to 70% of the 25.8 million adults and children in the U.S. with diabetes. U.S. (*Source: The Neuropathy Association*). In addition, there are 79 million individuals in the U.S. with pre-diabetes who are at risk for developing diabetic peripheral neuropathy (*Source: The Center for Disease Control*).

Living with neuropathy can cause tremendous frustration and social isolation for patients. The daily chronic pain impacts day-to-day functionality resulting in physical and psychological problems including impaired concentration, anxiety, depression, a decline in cognitive abilities, and sleep difficulties which in turn can lead to irritability and increased pain sensitivity.
Additionally, the economic burden from medical costs and workplace productivity losses are high and on the rise as the incidence of peripheral neuropathy increases. Neuropathic pain patients are often high health care system users as they seek relief from persistent suffering. Those debilitated by neuropathy or coping with chronic pain are challenged with working full-time and may become unemployable or stay under-employed.

DESCRIPTION & DEFINITION

Peripheral neuropathy describes damage to the peripheral nervous system, the vast communications network that transmits information from the brain and spinal cord (central nervous system) to every other part of the body. Peripheral nerves also send sensory information back to the brain and spinal cord, such as a message that the feet are cold, or a finger is burned. Damage to the peripheral nervous system interferes with these vital connections, distorting and sometimes interrupting messages between the brain and the rest of the body.

- Classification of the Peripheral Neuropathies

More than 100 types of peripheral neuropathy have been identified, each with its own characteristic set of symptoms, pattern of development and prognosis. Specific impaired function and symptoms depend on the type of nerves - motor, sensory, or autonomic - that are damaged:

- *Motor nerves* control movements of all muscles under conscious control, such as those used for walking, grasping things, or talking

- *Sensory nerves* transmit information about sensory experiences, such as the feeling of a light touch or the pain resulting from a cut.
- *Autonomic nerves* regulate biological activities that people do not control consciously, such as breathing, digesting food, and heart and gland functions.

➢ Forms of Neuropathy

- *Mononeuropathies*: Neuropathies that involve damage to only one nerve.
- *Polyneuropathies:* Neuropathies that involve multiple nerves affecting all limbs.
- *Mononeuritis multiplex:* Less commonly, neuropathies wherein two or more isolated nerves in separate areas of the body are affected

Some neuropathies affect all three types of nerves, but most often, neuropathies primarily affect one or two types. Therefore, neuropathies may be further described as predominantly motor neuropathy, predominantly sensory neuropathy, sensory-motor neuropathy, or autonomic neuropathy.

➢ Acute versus Chronic Neuropathies

In *acute neuropathies***,** such as Guillain-Barré syndrome, symptoms appear suddenly, progress rapidly, and resolve slowly as damaged nerves heal.

In *chronic neuropathies***,** symptoms begin subtly and progress slowly. There may be periods of relief followed by relapse. A plateau stage may be reached where symptoms stay the same for months or years. Some chronic neuropathies worsen over time, but fatality from neuropathy is extremely rare unless complicated by other diseases. Occasionally, neuropathy is a symptom of another disorder.

➢ Acquired peripheral neuropathies

Peripheral neuropathy may be either acquired or inherited.

➢ Acquired vs. inherited peripheral neuropathies

- *Acquired peripheral neuropathies* are grouped into three broad categories; those caused by:
  - ✓ *systemic disease*
  - ✓ *trauma from external agents*
  - ✓ *infections or autoimmune disorders affecting nerve tissue*

  Causes of *acquired peripheral neuropathy* include:
  - ✓ physical injury (trauma) to a nerve
  - ✓ tumors
  - ✓ toxins
  - ✓ autoimmune responses
  - ✓ nutritional deficiencies
  - ✓ alcoholism
  - ✓ vascular and metabolic disorders

- *Inherited forms of peripheral neuropathy* are caused by inborn mistakes in the genetic code or by new genetic mutations. Depending on the genetic error/mutation, inherited peripheral neuropathies can range from those with symptoms that begin in early adulthood and are minimal to more severe forms and symptoms/impairments that may begin in infancy or childhood. The most common inherited neuropathies are a group of disorders collectively referred to as *Charcot-Marie-Tooth disease* that result from flaws in genes responsible for manufacturing neurons or the myelin sheath and are characterized by extreme weakening and wasting of muscles in the lower legs and feet, gait abnormalities, loss of tendon reflexes, and numbness in the lower limbs.

➢ Diabetic Peripheral Neuropathy

Diabetic peripheral neuropathy is a chronic acquired form of nerve damage that can occur in individuals with diabetes. High blood sugar can injure nerve fibers throughout the body, but diabetic neuropathy most often damages nerves in the legs and feet.

ETIOLOGY

The primary cause of diabetic peripheral neuropathy is damage to nerve fibers and blood vessels from prolonged exposure to high blood sugar (glucose). While the precise mechanism for this damage remains unclear, a combination of factors likely plays a role, including the complex interaction between nerves and blood vessels. High blood glucose interferes with the ability of the nerves to transmit signals and weakens the walls of the small blood vessels (capillaries) that supply the nerves with oxygen and nutrients.

Other factors that may contribute to diabetic neuropathy include:

- *Inflammation in the nerves* caused by an autoimmune response that occurs when the immune system mistakenly attacks part of the body as if it were a foreign organism.
- Genetic factors unrelated to diabetes that make some people more susceptible to nerve damage.
- *Smoking and alcohol abuse* which damage both nerves and blood vessels and significantly increase the risk of infections.

Risk factors
Anyone with diabetes can develop neuropathy, but the following factors increase the risk of susceptibility to nerve damage:

- *Poor blood sugar control* is the greatest risk factor for every complication of diabetes, including nerve damage.
- *Duration of diabetes***.** The risk of diabetic neuropathy increases with increasing duration of diabetes, especially if there is also poo control of blood sugar. Peripheral neuropathy is most common in people who have had diabetes for at least 25 years.
- *Kidney disease.* Diabetes can cause damage to the kidneys, which may increase the toxins in the blood and contribute to nerve damage.
- *Smoking* narrows and hardens the arteries, reducing blood flow to the legs and feet, making it more difficult for wounds to heal and damages the integrity of the peripheral nerves.

PRESENTATION AND SYMPTOMS

- Early, primary symptoms of diabetic peripheral neuropathy may include**:**

  - tingling, prickling, buzzing, pinching or burning feeling in the feet
  - pins and needles in the feet
  - sharp, jabbing, stabbing pains
  - cramps in the legs and feet
  - cold sensation
  - numbness or reduced ability to feel pain or changes in temperature, especially in the feet and toes

  Symptoms often worsen at night.

- Progressive symptoms of diabetic peripheral neuropathy may include**:**

  - *Touch sensitivity:* heightened and/or extreme sensitivity to touch such as the weight of sheets or clothes being painful, or heightened tingling or numbness in the toes, feet, legs, or hands
  - *Muscle weakness***:** difficulty walking or getting up from a chair, grabbing things or carrying things with the hands as a result of muscle weakness from nerve damage
  - *Balance problems:* increased unsteadiness and incoordination when walking, occurring as the body adapts to changes brought on by muscle damage
  - *Serious foot problems:* such as ulcers, infections, deformities, and bone and joint pain

- Complications: Diabetic neuropathy can cause numerous serious complications. Among the most serious are the following two complications:

  - *Loss of a limb:* As nerve damage can cause lack of feeling in the feet, cuts and sores can go unnoticed and eventually become severely infected or ulcerated. The risk of infection is high because diabetes reduces blood flow to the feet. Infections that spread to the bone and cause tissue death (gangrene) may be impossible to treat and require amputation of a toe, foot or even the lower leg. More than half the non-traumatic lower limb amputations performed every year in the United States are due to diabetes.
  - *Charcot joint:* This occurs when a joint, usually in the foot, deteriorates because of nerve damage. Charcot joint is marked by loss of sensation, as well as swelling, instability and sometimes deformity in the joint itself.
  - *Neuropathic pain* is difficult to control and can seriously affect emotional well-being and overall quality of life. Neuropathic pain is often worse at night, seriously disrupting sleep and adding to the emotional burden of sensory nerve damage.

DIAGNOSIS

Patients being evaluated for diabetic peripheral neuropathy will have already been clinically diagnosed with diabetes and/or be evaluated for and diagnosed with diabetes prior to the evaluation for diabetic peripheral neuropathy.

Diabetic neuropathy is diagnosed by a qualified physician based on a thorough evaluation of the patient's symptoms, medical history and a physical exam that includes

assessment of blood pressure, heart rate, muscle strength and tone, tendon reflexes, and sensitivity to touch, position changes, temperature and vibration.
A comprehensive foot exam assessing the skin, muscles, bones, circulation, and sensation of the feet is also performed as part of the diagnostic process.

Specific tests that may be conducted as part of the diagnostic process include:

- *Filament test.* Sensitivity to touch may be tested using a soft nylon monofilament or via pin prick. The inability to feel the filament on the foot or the pin prick is a sign that sensation in those nerves has been lost or diminished.
- *Tuning fork*. A tuning fork is used for quantitative sensory testing to assess vibration and temperature change perception.
- *Nerve conduction studies or electromyography* are sometimes used to help determine the type and extent of nerve damage. Nerve conduction studies check the transmission of electrical current through a nerve. Electromyography evaluates how well muscles respond to electrical signals transmitted by nearby nerves. These tests are rarely needed to diagnose neuropathy.

CURRENT THERAPEUTIC APPROACHES TO THE MANAGEMENT OF CHRONIC PAINFUL DIABETIC PERIPHERAL NEUROPATHY

Nerve pain from diabetic peripheral neuropathy can be severe, constant, and difficult to treat. As diabetic neuropathy is a many-faceted complication of diabetes, it is often best managed symptomatically with an array of drugs and/or treatments. In addition to optimal management of blood glucose levels (including a regimen of diet, exercise and medication), the following medications and therapies, and combinations therein, are used to assist in the management of painful diabetic peripheral neuropathy symptoms:

(i) Over-the-counter (OTC) pain relief options:

- *OTC NSAIDs (nonsteroidal anti-inflammatory drugs),* such as aspirin, ibuprofen (Advil, Motrin), and naproxen (Aleve) reduce inflammation and relieve pain. A downside of NSAIDs is the potential for harmful side effects such as stomach irritation and bleeding, or even kidney and liver damage, with prolonged use, which may be more likely in people with diabetes.
- *Acetaminophen* medications relieve diabetes nerve pain without reducing inflammation and do not cause the stomach irritation of NSAIDs, but there is a risk of liver damage with excessive use.
- *Capsaicin* is found naturally in chili peppers or in drug stores under various brand names, including Capzasin-P and Zostrix. Capsaicin is believed to ease pain by reducing a chemical called substance P, which is involved in transmitting pain signals through the nerves. Effective on a short-term basis, there are concerns about long-term consequences such as prevention wound healing, which is most serious in patients with diabetes.
- *Lidocaine* is an OTC and/or prescription gel or cream anesthetic that numbs the area of application. Some product names include Topicaine and Xylocaine.
- *Other topical creams* such as salicylate, a chemical similar to aspirin found in pain-relieving creams like Aspercreme and Bengay; cortisone creams containing corticosteroids, potent anti-inflammatory drugs that can help relieve pain. However, there is no clear evidence that either helps relieve nerve pain from peripheral neuropathy.

(ii) Prescription pain relief options:

- *Prescription NSAIDs* such as Celebrex, Lodine, and Relafen. As with the OTC NSAIDs, people with diabetes are at greater risk of kidney damage that can occur with prescription NSAIDs, and at greater risk of heart disease which may also be elevated with prescription NSAID use.
- *Antidepressants*, such as:
  - ✓ *Tricyclic antidepressants (TCAs)* that primarily affect the levels of the brain chemicals norepinephrine and serotonin, such as Elavil, Pamelor and Norpramin. Side effects vary between the three, but can include drowsiness, weight gain, dry mouth, and dry eyes. For people with peripheral neuropathy, there may be additional side effects such as the development of blood pressure, heart rate problems and dizziness.
  - ✓ *Selective serotonin reuptake inhibitors (SSRIs)* that work by altering the amount of the brain chemical serotonin, but these are the least effective for pain management.
  - ✓ *Serotonin and norepinephrine reuptake inhibitors (SNRIs)*, such as Effexor and Cymbalta, affect the levels of the brain chemicals serotonin and norepinephrine. They are quite effective for pain relief with fewer side effects than the SSRIs or TCAs. Cymbalta is FDA-approved for painful neuropathy.
- *Antiseizure drugs* that prevent epileptic seizures can also relieve neuropathic pain by controlling the abnormal firing of nerve cells. These drugs include:
  - ✓ *Neurontin* is most commonly used for nerve pain from peripheral neuropathy. Side effects include causing sedation or dizziness at higher doses.
  - ✓ *Lyrica* is FDA-approved for painful neuropathy. The most common side effects are dizziness and sleepiness.
- *Opioid medicines* such as Ultram and Ultracet, are strong pain killers for when pain is very severe and immediate relief is needed. Ultram and Ultracet are FDA-approved painkillers that contain tramadol, a weak opioid (morphine-like) substance. The drug also weakly affects the brain chemicals serotonin and norepinephrine, similar to antidepressants, which reduces the perception of pain.
- *Tramadol* is often used as a back-up for "breakthrough pain" - pain that suddenly, for no apparent reason, is worse. Tramadol is a good replacement for over-the-counter medications at those times. However, strong narcotic opioid medications can cause severe constipation and have the potential for addiction.

(iii) Additional and Alternative Treatment Options:

- *Injections of local anesthetics such as lidocaine* - or patches containing lidocaine – can be used to numb the painful area for severe, intractable diabetes nerve pain.
- *Surgical destruction* of nerves or to relieve a nerve compression that causes pain.
- *Implantation of a device* that relieves pain.
- *Transcutaneous electrotherapy and percutaneous electrical nerve stimulation* are alternative therapies that provide electrical nerve stimulation wherein small amounts of electricity are used to block pain signals as they pass through the skin.
- *Hand or foot braces* to compensate for muscle weakness or to help relieve nerve compression.
- *Orthopedic shoes* to improve gait (walking) problems to will prevent foot injuries.

THEORY OF MECHANISM OF OPERATION OF THE APPLICATION OF LOW-LEVEL LASER THERAPY TO REDUCING PAIN

"Low-energy photon irradiation by low level laser light lasers or LED arrays has been found to modulate various biological processes in cell culture and animal models. This mechanism of photobiomodulation by LLLT lasers or LED arrays at the cellular level has been ascribed to the activation of mitochondrial respiratory chain components, resulting in initiation of a signaling cascade that promotes cellular proliferation and cytoprotection."
Source: Proc Natl Acad Sci U S A. 2003 Mar18; 100(6): 3439-44. 2003 Mar 07.

When applied to injuries and lesions, low level laser light has been shown to stimulate healing and to reduce pain by accelerating the speed, quality and strength of tissue repair and the reduction of inflammation. Furthermore, laser therapy has been found to be particularly effective over other standard therapies in relieving pain and other symptoms associated with injuries as it impacts the complete system of targeted muscles, tendons, ligaments, connective tissue, bone, nerve, and dermal tissues.

Lasers can strengthen damaged cells. Using photochemical processes, laser light inserts bio-photons into damaged cells. The cells begin to produce energy (ATP), which improves their function, assists their division, strengthens the body's immune system, and causes the secretion of various hormones. The tissues are healed, and pain diminishes. If damaged cells have died, the bio-photons help the division of neighboring cells, generating new tissues, and thus bring about healing.

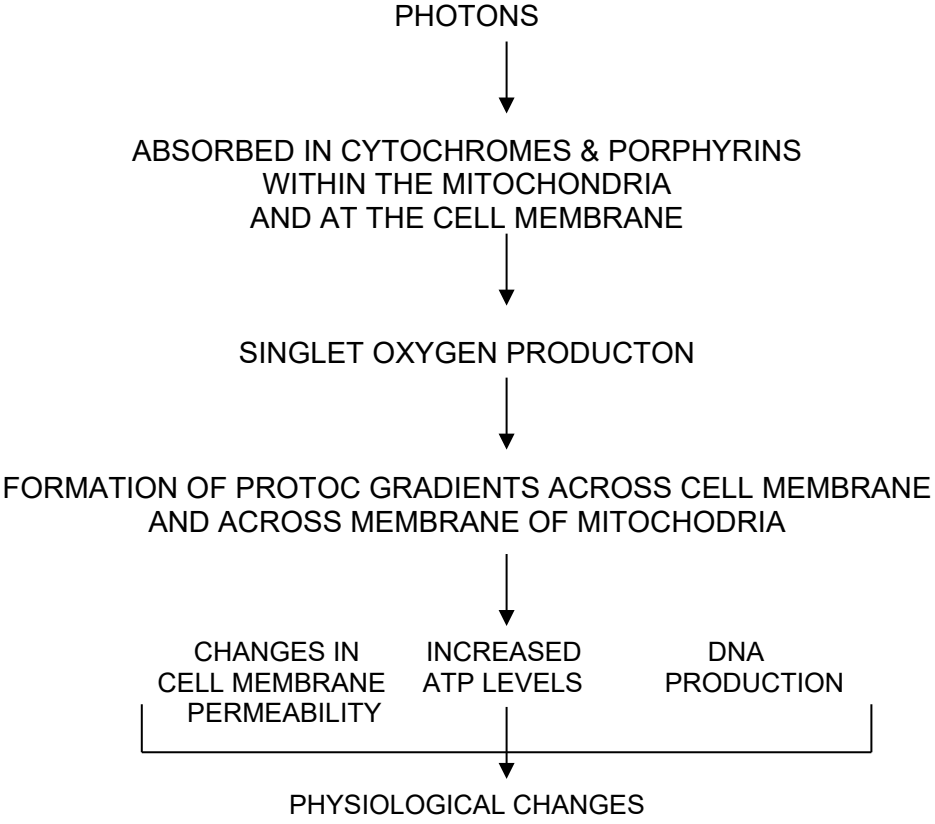
Therefore, LLLT promotes healing, regeneration and pain reduction through the following mechanisms:

1) increased cell membrane polarization and permeability
2) increased ATP production and respiratory chain activity
3) increased enzyme activity
4) increased collagen and epithelial production
5) increased capillary formation
6) increased macrophage (immune) activity
7) analgesic effects due to elevated endorphin production, electrolytic nerve blockage, and improved blood and lymph flow
8) anti-inflammatory effect due to improved circulation and accelerated tissue regeneration; and 9) increased production of antioxidants.

Of additional benefit is that light energy from low level lasers will only be absorbed by those cells and tissues that are not functioning normally and that need it. Soft laser light has no effect on healthy cells.

The progressive process by which low level laser light aids in the production of ATP, consequently providing cells with more energy which in turn optimizes the cells' condition to play their part in a natural healing and pain reduction process, is as follows:

The effects of low-level laser light are photo-chemical (not thermal), triggering normal cellular function.



THEORY OF MECHANISM OF OPERATION OF THE APPLICATION OF LOW-LEVEL LASER THERAPY TO REDUCING CHRONIC DIABETIC PERIPHERAL NEUROPATHY PAIN

Considering the general mechanism of operation of LLLT as explained above, it follows that LLLT provides relief from the foot pain from chronic diabetic peripheral neuropathy by:

- penetrating the skin of the foot and the ligaments and tendons to increase the production of ATP and activate enzymes in the targeted cells of the tissue to promote healing of the tendons and ligaments
- cultivating a growth factor response within the cells and tissue of the foot as a result of the increased ATP production to promote new, healthier cell and tissue growth to strengthen and support ligaments and tendons, to restore mechanical and sensory function, and to protect against further damage
- The anti-inflammatory properties of low-level lasers reduce nerve irritation and inflammation in the foot to provide pain relief

ERCHONIA CORPORATION LLLT LASER DEVICES AND PAIN REDUCTION INDICATIONS

Erchonia Corporation's 635nm red diode and 405nm violet diode low-level lasers have been shown through controlled clinical trials to be effective for pain reduction, as evidenced through the following FDA 510(k) approvals for various pain reduction indications based on the supportive outcome of those clinical trials.

1. **K191257:** *Erchonia® EVRL:* is indicated 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.

2. **K180197:** *Erchonia® FX-635:* is indicated for the following two indications:
   a. as an adjunct to provide relief of minor chronic low back pain of musculoskeletal origin.
   b. as an adjunct to reducing chronic heel pain arising from plantar fasciitis.

3. **K132940:** *Erchonia® Allay™:* is indicated as an adjunct to reducing chronic heel pain arising from plantar fasciitis.

4. **K072206:** *Erchonia® EML Laser:* is indicated for the temporary reduction in post-surgery pain at 24 hours after surgery following bilateral breast augmentation surgery.

5. **K041139:** *Erchonia® EML Laser*: is indicated as an adjunct to liposuction procedures of the thighs, hips and stomach for reduction of pain associated with the recovery process.

6. **K012580:** *Erchonia PL2000*: is indicated for adjunctive use in providing temporary relief of minor chronic neck and shoulder pain of musculoskeletal origin.

ADDITIONAL SUPPORTING LITERATURE

➢ **In vitro and in vivo optimization of infrared laser treatment for injured peripheral nerves.**
Anders JJ, Moges H, Wu X, Erbele ID, Alberico SL, Saidu EK, Smith JT, Pryor BA. Lasers Surg Med. 2014 Jan;46(1):34-45.

BACKGROUND AND OBJECTIVE: Repair of peripheral nerve injuries remains a major challenge in restorative medicine. Effective therapies that can be used in conjunction with surgical nerve repair to improve nerve regeneration and functional recovery are being actively investigated. It has been demonstrated by numerous peer reviewed publications that photobiomodulation (PBM) supports nerve regeneration, reinnervation of the denervated muscle, and functional recovery after peripheral nerve injury. However, a key issue in the use of PBM as a treatment for peripheral nerve injury is the lack of parameter optimization for any given wavelength. The objective of this study was to demonstrate that for a selected wavelength effective in vitro dosing, parameters could be translated to effective in vivo parameters.

MATERIALS AND METHODS: Comparison of infra-red (810 and 980 nm wavelengths) laser treatment parameters for injured peripheral nerves was done beginning with a series of in vitro experiments using primary human fibroblasts and primary rat cortical

neurons. The primary rat cortical neurons were used for further optimization of energy density for 980 nm wavelength light using measurement of total neurite length as the bioassay. For these experiments, the parameters included a 1 W output power, power density of 10 mW/cm(2) , and energy densities of 0.01, 0.1, 0.5, 2, 10, 50, 200, 1,000, and 5,000 mJ/cm(2) . For translation of the in vitro data for use in vivo it was necessary to determine the transcutaneous penetration of 980 nm wavelength light to the level of the peroneal nerve. Two anesthetized, male White New Zealand rabbits were used for these experiments. The output power of the laser was set at 1.0 or 4.0 W. Power density measurements were taken at the surface of the skin, sub-dermally, and at the level of the nerve. Laser parameters used in the in vivo studies were calculated based on data from the in vitro studies and the light penetration measurements. For the in vivo experiments, a total of 22 White New Zealand rabbits (2.34-2.89 kg) were used. Translated dosing parameters were refined in a pilot study using a transection model of the peroneal nerve in rabbits. Output powers of 2 and 4 W were tested. For the final set of in vivo experiments, the same transection nerve injury model was used. An energy density of 10 mW/cm(2) at the level of the peroneal nerve was selected and the laser parameters were further refined. The dosing parameters used were: 1.5 W output power, 43 seconds exposure, 8 cm(2) area and a total energy of 65 J.

RESULTS: In vitro, 980 nm wavelength light at 10 mW/cm(2) significantly improved neurite elongation at energy densities between 2 and 200 mJ/cm(2) . In vivo penetration of the infrared light measured in anesthetized rabbits showed that on average, 2.45% of the light applied to the skin reached the depth of the peroneal nerve. The in vivo pilot study data revealed that the 4 W parameters inhibited nerve regeneration while the 2 W parameters significantly improved axonal regrowth. For the final set of experiments, the irradiated group performed significantly better in the toe spread reflex test compared to the control group from week 7 post-injury, and the average length of motor endplates returned to uninjured levels.

CONCLUSION: The results of this study demonstrate that treatment parameters can be determined initially using in vitro models and then translated to in vivo research and clinical practice. Furthermore, **this study establishes that infrared light with optimized parameters promotes accelerated nerve regeneration and improved functional recovery in a surgically repaired peripheral nerve.** *PMID: 24338500*

- **Evaluation of low level laser therapy in reducing diabetic polyneuropathy related pain and sensorimotor disorders.**

Bashiri H.
Acta Med Iran. 2013 Sep 9;51(8):543-7.

Over the past three decades physicians have used light level laser therapy (LLLT) for the management and the treatment of diabetic peripheral neuropathy and have obtained results that call for further investigations. This study aimed to investigate the effectiveness of LLLT in treatment of pain symptoms in patients with diabetic polyneuropathy. In this study 60 patients with diabetic peripheral neuropathy were matched based on their sex, age, BMI, type of diabetes, duration of diabetes, and duration of pain, and randomized to case and control groups based on their established scores on the visual analog scale (VAS) and the Toronto clinical scoring system (TCSS). Cases received laser therapy with wavelength of 78 nm and 2.5 j/cm2 two times a week, each time for 5 min, for one month. During the same period, controls received sham laser therapy. Comparing the differences between the two groups' VAS and TCSS

mean scores before the intervention with that of the 2 weeks and 4 weeks after the intervention, we were able to see a statistically significant difference between the two groups (P<0.05). **Laser therapy resulted in improved neuropathy outcomes in diabetic patients who received it relative to the group that received sham therapy, evaluating before and after LLLT assessments**. Further studies are needed to test types of lasers, as well as different dosage and exposure levels required in different phase of neuropathic care, so as to obtain reproducible results.
PMID: 24026991

- **Effect of low-level laser therapy (LLLT) on acute neural recovery and inflammation-related gene expression after crush injury in rat sciatic nerve.**
Alcântara CC, Gigo-Benato D, Salvini TF, Oliveira AL, Anders JJ, Russo TL.
Lasers Surg Med. 2013 Apr;45(4):246-52.

BACKGROUND AND OBJECTIVES: Peripheral nerve function can be debilitated by different kinds of injury. Low-level laser therapy (LLLT) has been used successfully during rehabilitation to stimulate recovery. The aim of this study was to evaluate the effects of LLLT (660 nm, 60 J/cm(2) , 40 mW/cm(2)) on acute sciatic nerve injury.

MATERIALS AND METHODS: Thirty Wistar male rats were divided into three groups: (1) Normal, intact nerves; (2) I3d, crushed nerves evaluated on Day-3 post-injury; (3) I + L3d, crushed nerves submitted to two sessions of LLLT and investigated at 3 days post-injury. Sciatic nerves were removed and processed for gene expression analysis (real-time PCR) of the pro-inflammatory factors TWEAK, Fn14 and TNF-α and extracellular matrix remodeling and axonal growth markers, such as TIMP-1, MMP-2, and MMP-9. Zymography was used to determine levels of MMP-2 and MMP-9 activity and Western blotting was used to evaluate TNF-α protein content. Shapiro-Wilk and Levene's tests were applied to evaluate data normality and homogeneity, respectively. One-way ANOVA followed by Tukey test was used for statistical analysis with a significance level set at 5%.

RESULTS: An increase in TNF-α protein level was found in I + L3 compared to Normal and I3d ($P < 0.05$). Zymography showed an increase in proMMP-9 activity, in both I3d and I + L3d groups ($P < 0.05$). The increase was more evident in I + L3d ($P = 0.02$ compared to I3d). Active-MMP-9 isoform activity was increased in I + L3d compared to Normal and I3d groups ($P < 0.05$). Furthermore, the activity of active-MMP-2 isoform was increased in I3d and I + L3 ($P < 0.05$). An increase in TIMP-1 expression was observed in both I3d and I + L3d groups ($P < 0.05$).
CONCLUSIONS: The current study showed that LLLT increased MMPs activity, mainly MMP-9, and TNF-α protein level during the acute phase of nerve injury, modulating inflammation. Based on these results, it is recommended that LLLT should be started as soon as possible after peripheral nerve injury.
PMID: 23568823

- **Low-level laser therapy improves repair following complete resection of the sciatic nerve in rats.**
Medalha CC[1], Di Gangi GC, Barbosa CB, Fernandes M, Aguiar O, Faloppa F, Leite VM, Renno AC.
Lasers Med Sci. 2012 May;27(3):629-35.

The aim of this study is to analyze the effects of low-level laser therapy (LLLT) on the regeneration of the sciatic nerve in rats following a complete nerve resection. Male Wistar rats were divided into a control injury group, injury groups irradiated with a 660-nm laser at 10 or 50 J/cm(2), and injury groups irradiated with an 808-nm laser at 10 or 50 J/cm(2). Treatment began 24 h following nerve resection and continued for 15 days. Using the sciatic functional index (SFI), we show that the injured animals treated with 660 nm at 10 and 50 J/cm(2) had better SFI values compared with the control injury and the 808-nm groups. Animals irradiated with the 808-nm laser at 50 J/cm(2) show higher values for fiber density than do control animals. In addition, axon and fiber diameters were larger in animals irradiated with 660 nm at 50 J/cm(2) compared to the control group. **These findings indicate that 660-nm LLLT is able to provide functional gait recovery and leads to increases in fiber diameter following sciatic nerve resection.**
PMID: 22009383

- **Effects of 660 and 780 nm low-level laser therapy on neuromuscular recovery after crush injury in rat sciatic nerve.**

Gigo-Benato D, Russo TL, Tanaka EH, Assis L, Salvini TF, Parizotto NA.
Lasers Surg Med. 2010 Nov;42(9):673-82.

BACKGROUND AND OBJECTIVE: Post-traumatic nerve repair is still a challenge for rehabilitation. It is particularly important to develop clinical protocols to enhance nerve regeneration. The present study investigated the effects of 660 and 780 nm low-level laser therapy (LLLT) using different energy densities (10, 60, and 120 J/cm²) on neuromuscular and functional recovery as well as on matrix metalloproteinase (MMP) activity after crush injury in rat sciatic nerve.

MATERIALS AND METHODS: Rats received transcutaneous LLLT irradiation at the lesion site for 10 consecutive days post-injury and were sacrificed 28 days after injury. Both the sciatic nerve and tibialis anterior muscles were analyzed. Nerve analyses consisted of histology (light microscopy) and measurements of myelin, axon, and nerve fiber cross-sectional area (CSA). S-100 labeling was used to identify myelin sheath and Schwann cells. Muscle fiber CSA and zymography were carried out to assess the degree of muscle atrophy and MMP activity, respectively. Statistical significance was set at 5% ($P \leq 0.05$).

RESULTS: Six hundred sixty nanometer LLLT either using 10 or 60 J/cm² restored muscle fiber, myelin and nerve fiber CSA compared to the normal group (N). Furthermore, it increased MMP-2 activity in nerve and decreased MMP-2 activity in muscle and MMP-9 activity in nerve. In contrast, 780 nm LLLT using 10 J/cm² decreased MMP-9 activity in nerve compared to the crush group (CR) and N; it also restored normal levels of myelin and nerve fiber CSA. Both 60 and 120 J/cm² decreased MMP-2 activity in muscle compared to CR and N. 780 nm did not prevent muscle fiber atrophy. Functional recovery in the irradiated groups did not differ from the non-irradiated CR.

CONCLUSION: Data suggest that 660 nm LLLT with low (10 J/cm²) or moderate (60 Jcm²) energy densities is able to accelerate neuromuscular recovery after nerve crush injury in rats.
PMID: 20976807

- **Chapter 25: Phototherapy in peripheral nerve injury: effects on muscle preservation and nerve regeneration**.
Rochkind S, Geuna S, Shainberg A.
Int Rev Neurobiol. 2009;87:445-64.

Post-traumatic nerve repair and prevention of muscle atrophy represent a major challenge of restorative medicine. Considerable interest exists in the potential therapeutic value of laser phototherapy for restoring or temporarily preventing denervated muscle atrophy as well as enhancing regeneration of severely injured peripheral nerves. Low-power laser irradiation (laser phototherapy) was applied for treatment of rat denervated muscle in order to estimate biochemical transformation on cellular and tissue levels, as well as on rat sciatic nerve model after crush injury, direct or side-to-end anastomosis, and neurotube reconstruction. Nerve cells' growth and axonal sprouting were investigated in embryonic rat brain cultures. The animal outcome allowed clinical double-blind, placebo-controlled randomized study that measured the effectiveness of 780-nm laser phototherapy on patients suffering from incomplete peripheral nerve injuries for 6 months up to several years. In denervated muscles, animal study suggests that the function of denervated muscles can be partially preserved by temporary prevention of denervation-induced biochemical changes. The function of denervated muscles can be restored, not completely but to a very substantial degree, by laser treatment initiated at the earliest possible stage post injury.
In peripheral nerve injury, laser phototherapy has an immediate protective effect. It maintains functional activity of the injured nerve for a long period, decreases scar tissue formation at the injury site, decreases degeneration in corresponding motor neurons of the spinal cord, and significantly increases axonal growth and myelinization. In cell cultures, laser irradiation accelerates migration, nerve cell growth, and fiber sprouting. In a pilot, clinical, double-blind, placebo-controlled randomized study in patients with incomplete long-term peripheral nerve injury, 780-nm laser irradiation can progressively improve peripheral nerve function, which leads to significant functional recovery. A 780-nm laser phototherapy temporarily preserves the function of a denervated muscle, and accelerates and enhances axonal growth and regeneration after peripheral nerve injury or reconstructive procedures. Laser activation of nerve cells, their growth and axonal sprouting can be considered as potential treatment for neural injury. Animal and clinical studies show the promoting action of phototherapy on peripheral nerve regeneration, which makes it possible to suggest that the time for broader clinical trials has come.
PMID: 19682654

- **Laser phototherapy (780 nm), a new modality in treatment of long-term incomplete peripheral nerve injury: a randomized double-blind placebo-controlled study.**
Rochkind S[1], Drory V, Alon M, Nissan M, Ouaknine GE.
Photomed Laser Surg. 2007 Oct;25(5):436-42.

OBJECTIVE: The authors conducted this pilot study to prospectively investigate the effectiveness of low-power laser irradiation (780 nm) in the treatment of patients suffering from incomplete peripheral nerve and brachial plexus injuries for 6 months up to several years.

BACKGROUND DATA: Injury of a major nerve trunk frequently results in considerable

disability associated with loss of sensory and motor functions. Spontaneous recovery of long-term severe incomplete peripheral nerve injury is often unsatisfactory.

METHODS: A randomized, double-blind, placebo-controlled trial was performed on 18 patients who were randomly assigned placebo (non-active light: diffused LED lamp) or low-power laser irradiation (wavelength, 780 nm; power, 250 mW). Twenty-one consecutive daily sessions of laser or placebo irradiation were applied transcutaneously for 3 h to the injured peripheral nerve (energy density, 450 J/mm(2)) and for 2 h to the corresponding segments of the spinal cord (energy density, 300 J/mm(2)). Clinical and electrophysiological assessments were done at baseline, at the end of the 21 days of treatment, and 3 and 6 months thereafter.

RESULTS: The laser-irradiated and placebo groups were in clinically similar conditions at baseline. The analysis of motor function during the 6-month follow-up period compared to baseline showed statistically significant improvement ($p = 0.0001$) in the laser-treated group compared to the placebo group. No statistically significant difference was found in sensory function. Electrophysiological analysis also showed statistically significant improvement in recruitment of voluntary muscle activity in the laser-irradiated group ($p = 0.006$), compared to the placebo group.

CONCLUSION: This pilot study suggests that **in patients with long-term peripheral nerve injury, noninvasive 780-nm laser phototherapy can progressively improve nerve function, which leads to significant functional recovery.**
PMID: 17975958

- **Promotion of regenerative processes in injured peripheral nerve induced by low-level laser therapy.**

Mohammed IF, Al-Mustawfi N, Kaka LN.
Photomed Laser Surg. 2007 Apr;25(2):107-11.

OBJECTIVE: This study aimed to assess in vitro the influence of low-level laser therapy (LLLT) on the regenerative processes of a peripheral nerve after trauma.

BACKGROUND DATA: In peripheral nerve injury initiated after severing due to accident or by a surgeon during operation, photomodulation by light in the red to near-infrared range (530-1000 nm) using low-energy lasers has been shown to accelerate nerve regeneration.

METHOD: Twenty-four New Zealand adult male rabbits were randomly assigned to two equal groups (control and laser-treated). General anesthesia was administered intramuscularly, and exploration of the peroneal nerve was done in the lateral aspect of the left leg. Complete section of the nerve was performed, which was followed by suturing of the neural sheath (epineurium). Irradiation was carried out directly after the operation and for 10 consecutive days. The laser used was diode with wavelength of 901 nm (impulsive) and power of 10 mW; it was a square-shaped window type (16 cm(2)), and its energy was applied by direct contact of the instrument's window to the site of the operation. Three rabbits from each group were sacrificed at the end of weeks 2, 4, 6, and 8, and specimens were collected from the site of nerve suturing and sent for histopathological examination.

RESULTS: Two important factors were examined via histopathology: diameter of the nerve fibers and individual internodal length. **Compared to the control group, significant variations in regeneration were observed, including thicker nerve fibers, more regular myelin layers, clearer nodes of Ranvier with absence of short nodes in the treated group.** Variations between the two groups for diameter were significant for the 2(nd) week ($p < 0.05$), highly significant for the 4(th) and 6(th) weeks, respectively ($p < 0.01$), and very highly significant for the 8(th) week ($p < 0.001$). Variations between the two groups for internodal length were highly significant for the 2(nd) and 4(th) weeks ($p < 0.01$), and very highly significant for the 6(th) and 8(th) weeks ($p < 0.001$).

CONCLUSION: This experiment affirms the beneficial effect of LLLT on nerve regeneration, since LLLT produced a significant amount of structural and cellular change. The results of the present study suggest that laser therapy may be a viable approach for nerve regeneration, which may be of clinical relevance in scheduled surgery or microsurgery.
PMID: 17508846

STUDY RATIONALE & JUSTIFICATION

The chronic pain of diabetic peripheral neuropathy can be debilitating, impacting the individual's day-to-day functionality that further leads to physical, cognitive, psychological, sleep and social impairments. Additionally, diabetic neuropathic pain patients are typically burdensome to the health care system, frequently seeking relief from the persistent pain. Many afflicted also suffer economically, as coping with the chronic pain of the condition may render them unemployable or under-employed.

Current therapeutic approaches for managing the chronic pain of diabetic peripheral neuropathy are primarily over-the-counter and prescription medications. However, in addition to their general limited effectiveness, many have harmful side effects with prolonged use such as stomach irritation and bleeding, kidney and liver damage, prevention of wound healing, elevated blood pressure and heart rate problems which can be both more likely to occur and more likely to pose serious implications for individuals with diabetes. Additional potential side effects include dizziness, drowsiness, weight gain, dry mouth, and dry eyes, as well as the potential for addiction with certain prescription medications. Non-medication alternatives are also of limited effectiveness and most, including injections of local anesthetics, surgical destruction of nerves, device implantation and transcutaneous electrotherapy and percutaneous electrical nerve stimulation are costly, invasive and carry their owns set of potentially harmful and lasing side effects.

Low level laser light therapy, such as that provided through application of the Erchonia® EVRL OTC™ Laser as proposed in this study protocol, offers a simple, quick, non-invasive, safe, effective and side-effect free option to reduce diabetic peripheral neuropathy pain. Prior trials with Erchonia low level lasers have demonstrated their efficacy in reducing chronic pain in various clinically diagnosed chronic pain conditions, and in post-surgical pain, in a clinically meaningful and statistically significant manner, as is the treatment goal being evaluated in the current clinical study.

Specific Justification for the use of the Erchonia® EVRL OTC™ device for Over-the-Counter application to reduce chronic pain arising from diabetic peripheral neuropathy is found through the following FDA clearances for Erchonia® low level laser devices for chronic pain reduction indications. Each device of which was considered a non-significant risk (NSR), and there were no reported side effects related to the device treatment(s).

1. **K180197:** *Erchonia® FX-635:* is indicated for the following two indications:
   a. as an adjunct to provide relief of minor chronic low back pain of musculoskeletal origin.
   b. as an adjunct to reducing chronic heel pain arising from plantar fasciitis.
2. **K132940:** *Erchonia® Allay™:* is indicated as an adjunct to reducing chronic heel pain arising from plantar fasciitis.
3. **K072206:** *Erchonia® EML Laser:* is indicated for the temporary reduction in post-surgery pain at 24 hours after surgery following bilateral breast augmentation surgery.
4. **K041139:** *Erchonia® EML Laser*: is indicated as an adjunct to liposuction procedures of the thighs, hips and stomach for reduction of pain associated with the recovery process.
5. **K012580:** *Erchonia PL2000*: is indicated for adjunctive use in providing temporary relief of minor chronic neck and shoulder pain of musculoskeletal origin.
6. **K191257:** *Erchonia® EVRL:* is indicated 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.

LLLT is as safe as it is effective, there are no known side effects of this form of light therapy. The only known potential adverse event associated with the use of laser devices is that long-term exposure to laser light could cause damage to eyesight. As a precaution, during all laser treatment administrations with the Erchonia® EVRL OTC the subject will wear safety glasses that filter out the laser light spectrum. There are no other known potential adverse events from application of the study lasers. There have been no observed or reported adverse events or reactions to the application of the family of Erchonia® laser devices in several other studies using these laser devices.

Previous, Over the Counter (OTC) use of the Erchonia laser has been proven in a lay person (non-doctor) usability and efficacy clinical trial which received FDA OTC clearance under 510(k) # **K162578 and K143007**. In this clinical study the lay person was provided a device operational manual for guidance on the treatment protocol and administration, no training was provided by the study sponsor.

Results showed device operation by the lay persons achieved equal or greater circumference reduction (6.2”) compared to the device administration from a licensed physician (3.54”), in the previous prescription-based FDA study using the identical device. Thus, proving the lay person’s ability to safely and correctly administer the Erchonia laser treatment.

STUDY DESIGN

This pilot study is a non-blinded, single group evaluation of the effect of the Erchonia® EVRL OTC™ on providing relief from chronic pain arising from diabetic peripheral neuropathy.

SUBJECT GROUP

All subjects will be test subjects; that is, all study subjects will receive the active Erchonia® EVRL OTC laser treatment.

NON-BLINDED DESIGN

This pilot study will be non-blinded, such that both subjects and the investigator(s) will be aware that they are receiving the study procedures with active (true) Erchonia® EVRL OTC laser device.

NON-RANDOMIZED

This pilot study is a non-randomized design, wherein all subjects receive the active procedure administrations and the same treatment protocol.

COMPENSATION

A subject will not receive financial compensation for his or her participation in this clinical study.

A subject will not be charged for the cost of the study procedures with the Erchonia® EVRL OTC™ 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.

SAMPLE SIZE

There will be 10 qualified subjects enrolled in this pilot study.

STUDY PROCEDURE

STUDY TEST BATTERY

The following is a list and description of the study assessment tools to be used and the variables to be recorded in this clinical study. At each evaluation point, the precise tools and variables from this list that will be employed will be specified.

BASELINE VARIABLES

A. Neuropathy Variables

- Number of months/years since onset of foot pain.
- Number of months/years since diabetes diagnosis
- Insulin dependency

B. Medication and Treatment

- *Prior treatment approaches for* diabetic peripheral neuropathy foot pain*:* Record all prior treatments, whether conventional or alternative, tried by the subject for pain reduction.
- *Concomitant Medication and Therapy Use:* Record all over-the-counter and prescription medications currently used for any indication (other than the management of neuropathy pain symptoms)

***C. Subject Demographics*:** Subject age, gender and ethnicity are recorded.

OUTCOME ASSESSMENT TOOLS

Numerical Rating Scale (NRS)

The Numerical Rating Scale (NRS) will be used to capture the self-reported daily impact of the subject's foot pain. With 1 being "No Pain" and 100 being "Worst possible Pain

NUMERICAL RATING SCALE: FOOT PAIN

How does the subject rate his or her Foot Pain on a scale of 1 to 100? With 1 being "No Pain" and 100 being "Worst possible Pain".

FOOT PAIN SCORE: _____/100

Subject Satisfaction with Study Outcome

The subject is asked to rate how satisfied he or she is with any change in his or her overall foot pain following completion of the laser administration procedures with the Erchonia® EVRL OTC™ by using the 5-point Likert scale presented below to respond to the following question: "Overall, how satisfied or dissatisfied are you with any change in your foot pain following the study procedures with the study laser device?"

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

STUDY PROCEDURE PROTOCOL

STUDY QUALIFICATION

SIGNING OF INFORMED CONSENT FORM

The potential participant will be sent an electronic informed consent (eIC) in accordance to *"FDA Guidance for Institutional Review Boards, Investigators, and Sponsors, Use of Electronic Informed Consent, Questions and Answers, December 2016"*. It is the responsibility of the Study Investigator to obtain the eIC. The subject will be provided sufficient opportunity to consider whether to participate (see 45 CFR 46.116 and 21 CFR 50.20). This may be accomplished by discussions with the study investigator through a combination of electronic messaging, telephone calls, video conferencing, or a live chat. When live chat or video conferencing is used during the eIC process, the study investigator will remind subjects to conduct the eIC discussion in a private location to help ensure privacy and confidentiality.

The potential participant must be willing to provide electronic signature in the provided econsent platform that is 21 CFR Part 11 complaint and include a method for verifying identity, such as a birth certificate, government-issued passport, or a driver's license.

ASSIGNMENT OF SUBJECT IDENTIFICATION NUMBER

The subject is assigned a unique subject identification number based upon 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 CHECKLIST

In order to be eligible for study participation a subject the following qualifications must be met:

INCLUSION CRITERIA PART 1

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

- Previously diagnosed with diabetes induced Peripheral Neuropathy by a qualified health Physician.
- Over the age of 18 years of age
- Able to read and write English.
- Constant feet pain on-going over at least the past 3 months.
- Subject is willing and able to refrain from consuming any OTC and/or prescription medications including muscle relaxants and/or herbal supplements and/or recreational and medical drugs including cannabis intended for the relief of pain and/or inflammation throughout the course of study participation, except for the study-specific pain relief medication of OTC Tylenol.

- Subject is willing and able to refrain from engaging in any non-study procedure therapies for the management of foot 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.
- Self-reported foot pain on the Numerical Rating Scale (NRS) is 50 or greater

EXCLUSION CRITERIA

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

- Pregnant or think you might be pregnant.
- Open wounds (sores, cuts, ulcers, etc) around the feet
- Cancerous growths around the feet

PRE-PROCEDURE ACTIVITES

DEVICE SHIPMENT

The qualified subject will be shipped a Erchonia® EVRL OTC™ device, that is preset and cannot be altered by the end user. Additionally, the subject will be shipped Erchonia® EVRL OTC™ Operation Manual and Treatment Log Form.

PRE-PROCEDURE EVALUATION PHASE

The pre-procedure evaluation phase commences following the delivery of the Erchonia® EVRL OTC™ device to the subject. During pre-procedure evaluation, the following is recorded over videoconference or telemedicine:

BASELINE VARIABLES

- Baseline Foot Variables
- Baseline Concomitant Medication and Therapy Use
- Subject Demographics

PRE-PROCEDURE OUTCOME ASSESSMENTS

- Numerical rating scale: Foot pain

PROCEDURE ADMINISTRATION PROTOCOL

- The procedure administration phase of the study commences following completion of the pre-procedure phase, on the same day or up to 15 days later.
- The procedure administration phase extends over 3 consecutive weeks.

- Each subject receives 42 total procedures with the Erchonia® EVRL OTC™: twice daily procedure administrations for 3 weeks.
- Each procedure administration lasts 10 minutes.
- Each procedure administration is competed at the subject's home.
- Each subject will be provided a "Operation Manual" that details the laser use and treatment administration.
- Each subject will be provided a "Treatment Log Form" to document each time the treatment is administered.

- **Procedure administration protocol is as follows:**

1. The subject seats comfortably in a chair and is correctly fitted with the provided safety goggles.

2. The Erchonia® EVRL OTC™ laser is held at the top of the right foot, at a distance of approximately 3-6 inches from the skin throughout the entire treatment.
   Note: The laser lights will cover the top of ankle joint and beyond the toes. *(shown in Fig 2)*

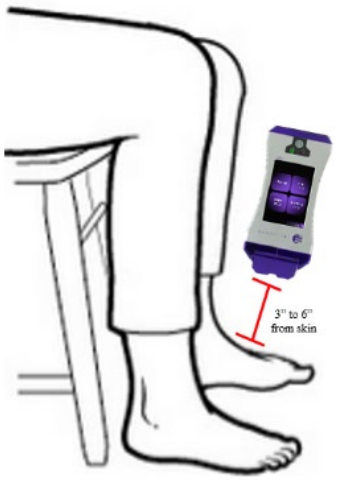


Fig 1. Treatment

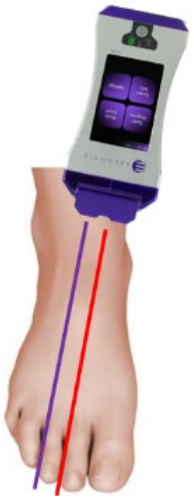


Fig 2. Treatment Close Up

3. The Erchonia® EVRL OTC™ is then activated for 5 minutes.
4. Step 2-3 is then repeated over the left foot. Both the right and left foot will receive 5-minute treatment each.
5. The subject's protective eyewear is then removed, and the session is over.

PROCEDURE ADMINISTRATION PHASE MEASURES

1 WEEK EVALUATION

Following 1 week of study procedure administrations with the Erchonia® EVRL OTC™, the following will be recorded over phone call or videoconference with the investigator and subject:

- Numerical rating scale: Foot pain
- Adverse Events Evaluation

2 WEEK EVALUATION

Following 2 weeks of study procedure administrations with the Erchonia® EVRL OTC™, the following will be recorded over phone call or videoconference with the investigator and subject:

- Numerical rating scale: Foot pain
- Adverse Events Evaluation

3 WEEK EVALUATION: STUDY ENDPOINT

Following 3 weeks of study procedure administrations with the Erchonia® EVRL OTC™, the following will be recorded over phone call or videoconference with the investigator and subject as outlined in the STUDY TEST BATTERY section above. These recordings will form the study endpoint data set from which change from baseline will be evaluated with respect to assessing study outcome.

- Numerical rating scale: Foot pain
- Subject Satisfaction with Study Outcome
- Adverse Events Evaluation

POST- TREATMENT EVLAUATION PHASE

WEEK 7: POST TREATMENT FOLLOWUP

Four weeks following completion of the 3-week Treatment Phase (7 weeks after study onset), the following will be recorded over phone call or videoconference with the investigator and subject:

- Numerical rating scale: Foot pain
- Subject Satisfaction with Study Outcome
- Adverse Events Evaluation

ADVERSE EVENTS

At any time throughout the duration of the clinical trial that is necessary, any and all potential adverse events reported by a subject will be reported to the investigator and will be recorded on the case report form, and subsequently evaluated by a suitably qualified independent reviewer for determination of relationship to the study treatment and whether

or not 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 have not typically yielded any adverse events or reactions. However, potential adverse events that may feasibly occur from application of the Erchonia® EVRL OTC™ include, but are not necessarily limited to: skin irritation, discoloring, rash, indentations and infection.

PRIVACY AND CONFIDENTIALITY

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

Copies of all subject case report forms will be made and supplied to Regulatory Insight, Inc. Regulatory Insight, Inc. will maintain these copies in a separate clinical study file that is kept in a locked filing cabinet on their respective premises. The original records will be maintained at the respective test site.

Subjects' identities will be kept confidential by assigning each subject a subject ID upon acceptance into the study. The subject ID will comprise the investigator's two initials (first and last name initials) and a three-digit number that will be based upon the subject's order of entry into the clinical study. For example, with Investigator John Black would have a subject ID of JB101-JB110. Regulatory Insight, Inc. will receive no additional identifying information about a subject and will therefore have no way of linking a subject ID to a particular subject and his or her results.

MONITORING OF THE CLINICAL STUDY

Prior to commencement of the study, the trained study Monitor(s) will provide formalized and documented training to the conduct of clinical studies in general, to the specifics of the current clinical study protocol, to the identification and reporting of adverse events and protocol deviations and to the correct set-up, operation and treatment application of the Erchonia® EVRL OTC to the study population for all involved parties. A formalized Clinical Trial Monitoring Plan will be in place that will be strictly followed to ensure on-going compliance and accuracy of procedures.

STATISTICAL ANALYSIS

No Statistical Analysis. As this is an observational pilot study only, there are no pre-established primary or secondary outcome measures and no pre-established individual subject or study success criteria; rather it is the goal of this study to explore the potential benefits of low level laser therapy administration with the Erchonia EVRL OTC™ in reducing chronic pain associated with peripheral neuropathy, the results of which may be used to assist in developing a controlled clinical study to formally evaluate the study goal in the future.

END OF DOCUMENT