MODEL: ERCHONIA® HLS

TRADE NAME: SPECTRUM BY ERCHONIA™

A double-blind, placebo-controlled randomized evaluation of the effect of the Erchonia® HLS laser device on children with autistic disorder clinical study protocol 2

ERCHONIA CORPORATION

Version 1.3
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TABLE OF CONTENTS

STUDY INFORMATION

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PURPOSE OF STUDY
The purpose of this clinical study is to demonstrate the efficacy of the Erchonia® HLS laser device, manufactured by Erchonia Corporation (the Sponsor), for the treatment of symptoms of irritability associated with autistic disorder in children aged five to twelve years, inclusive.

The Sponsor intends to submit the data and analysis from this study via a de novo application to obtain FDA clearance to market the laser device for the intended indication.

LABELING
Once cleared for market in the U.S., the Erchonia® HLS laser device will be labeled as prescription device, per 21 CFR § 801.109.

INDICATION FOR USE
The results of this clinical study will be used to support the following indication for use: "The Erchonia® HLS laser device is indicated to improve the symptoms of irritability associated with autistic disorder in children aged five to twelve years, inclusive."

REGULATORY HISTORY
This clinical study protocol design is a cumulative result of the following regulatory history.

1. **FDA Pre-IDE#I120613** review of the following protocol: The Erchonia® HLS Laser Device: A double-blind, placebo-controlled randomized evaluation of the effect of the Erchonia® HLS laser device on children and adolescents with autistic disorder clinical study protocol; *Version 1.1, June 26, 2012; Sponsor: Erchonia Corporation.*

   (i) Submitted to the FDA by the Sponsor on 7/15/12
   (ii) FDA's written review received by the Sponsor on 1/17/13
   (iii) Sponsor response submitted to FDA on 2/5/13 along with the requested Supplement protocol (V2.0 1/31/13) reviewed as **Q130138**
   (iv) FDA's written review for Q130138 received by the Sponsor on 4.23.13

2. **DEN180046:** De Novo submission to FDA made by the Sponsor on 8/28/18 supported by the results of the clinical study based on the outcome of the FDA's written review of Q130138.

(i) Two rounds of FDA Interactive Review questions ensued with responses submitted by the Sponsor within the requested timeframe in both instances
(ii) FDA's written Request for Additional Information (RAI) received by the Sponsor on 1/23/19
(iii) Sponsor's response to the RAI submitted on 2/26/19
(iv) FDA Denial of De Novo request received by the Sponsor on 5/22/19

FDA Pre-Sub Q191179 review of the following protocol: A double-blind, placebo-controlled randomized evaluation of the effect of the Erchonia® HLS laser device on children with autistic disorder clinical study protocol 2; version 1.0, June 10, 2019.
(i) Submitted to the FDA by the Sponsor on 6/10/19
(ii) FDA's written review received by the Sponsor on 8/22/19
(iii) Face-to-Face Meeting between the Sponsor and FDA to attain clarification of certain items in FDA's written review written review was conducted on 12/06/2019.
(iv) Meeting Minutes provided by the Sponsor to the FDA on 12/11/2019.

This current study protocol represents the modified protocol inclusive of resolutions of all protocol deficiencies and items noted by the FDA through DEN180046 and Q191179.

LANGUAGE TRANSLATIONS
For the intended test site in Mexico, every document in this study will be provided to that test site in Spanish (Mexico). These certified translations will come from the following various sources, as applicable, and as specifically identified within each relevant section below.

1. **Available published translations** distributed through certified U.S. distributors: study diagnostic and assessment tools listed in the Study Test Battery section.

2. **Language Scientific, Inc.,** a U.S.-based technical and medical translation company located in Medford, MA (www.languagescientific.com) who has been providing medical and clinical research translation services to the clinical research industry for over 15 years in over 215 languages with clients including the U.S. Government organizations, Quintiles, PharmaNet, Bioclinica, and PRA International. A notarized Certification of Translation Accuracy will be provided for each individual English to Spanish translated document.

   Documents that will be translated from English to Spanish (Mexico) and certified by Language Scientific are the following:
   - Some assessment tools
   - Study protocol
   - Study case report forms (CRFs)
   - Regulatory and Training documentation
   - Device information supplied

3. **Western Institutional Review Board (WIRB),** located in Puyallup, WA 98374 (www.wirb.com) translation services department will translate the WIRB-approved consent form from English to Spanish (Mexico) and will supply a signed translator certification statement.

Study staff at the test site will record the information on the relevant documents, including the CRFs in Spanish. Subsequent to completion of the trial, the Sponsor will have the Spanish recordings translated into English and entered in the corresponding English document versions by Language Scientific, Inc., with an accompanying Certification of Translation Accuracy.

CLINICAL TRIAL APPROVAL
The clinical study and test site/PI will operate under approval from a U.S.-based Institutional Review Board and any applicable local Ethics Committee.

The U.S.-based IRB will be the Western Institutional Review Board® (WIRB®), as listed above. The local Ethics Committee, if applicable, is yet to be determined.

TREATMENT DEVICE INFORMATION: ERCHONIA® HLS LASER

DEVICE DESCRIPTION

The Erchonia® HLS Laser will be administered to the subject by the investigator at the test site for a total of 8 treatment administrations: 2 administrations per week for 4 consecutive weeks, each treatment administration 3-4 days apart. Each HLS administration will last 5 minutes.

The Erchonia HLS Laser is a hand-held dual diode, variable hertz laser that is portable, self-contained, lightweight, and battery operated.

The Erchonia HLS Laser emits a 640 nanometer (nm) wavelength with a tolerance of ±10 nanometer, from each of the two laser diodes. The diodes are classified by the Center for Devices and Radiological HHLSth (CDRH) as Class II laser diodes in accordance with IEC 60825-1, compliant to 21CFR1040 via Laser Notice#50.

An internal battery that is recharged using an external inductive charging base powers the laser. The internal battery powers the two specially created and patented electronic diodes that emit a <10mW red laser beam.

The HLS Laser has the following specifications:

Power	7.5 mW ± 1.00 mW
Wavelength	640 nm ± 10 nm
Waveform	Variable Hertz
Joules	2.10 Joules per treatment administration
Energy Source	Dual electronic diodes, with patented optics
Power Supply	100-240 V ac; 50-60 Hz electrical outlet, lithium-ion Polymer battery
Duty Cycle	50%
Energy Delivery	Handheld treatment probe
Treatment Time	0 – 9.9 minutes
Target Size	Line pattern, manually scanned over area of treatment

DEVICE SPECIFICATIONS

Figure 1 below contains an image of the Erchonia HLS Laser, and a description of the system components follows.

Figure 1: The Erchonia HLS Laser

#1 POWER BUTTON (ON/OFF)

The Power Button allows you to turn the device ON "|" or OFF "O". To turn the device ON, press and hold this button until the green (#3 Power On Light) turns on. To turn off the device it is recommended to use the **"Power Down"** icon on the **"Function Screen".** Refer to the Powering Down section. In the unlikely event that your device stops responding to touches, by pressing and holding the power button for 10 seconds will force shut down the device. This is only recommended if the device cannot be turned off from the **"Power Down"** screen.

#2 LASERS ON LIGHT

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

#3 POWER ON LIGHT

The Power On LED indicator will display a constant green light when the device is powered on.

#4 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.

#5 PIVOTING LASER MOUNT

The Pivoting Laser Mount allows the user to adjust the laser angle based on user preference.

#6 LASER DIODES

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 red beam(s). This is a specially designed and patented unit created to ensure the laser beam is focused and directed for the most optimal use.

CHARGER BASE AND POWER SUPPLY

The Erchonia HLS Laser contains a unique battery system designed by specification to provide the end user with a constant and consistent power, capable of intense use for extended periods, while yet being lightweight for portability. The battery system encompasses the internal battery component, the inductive charger base, and the external power supply. The internal battery is sHLSed by the vendor and then encased within the device housing and can only be replaced by the manufacturer. The battery component is refreshed by the use of an external power supply used with the charger base. The power supply is an IEC 60601 3rd Ed. certified unit, compliant to CE/CB standards.

Figure 2 below contains an image of the Erchonia HLS Laser charger base and power supply, and a description of the system components follows.

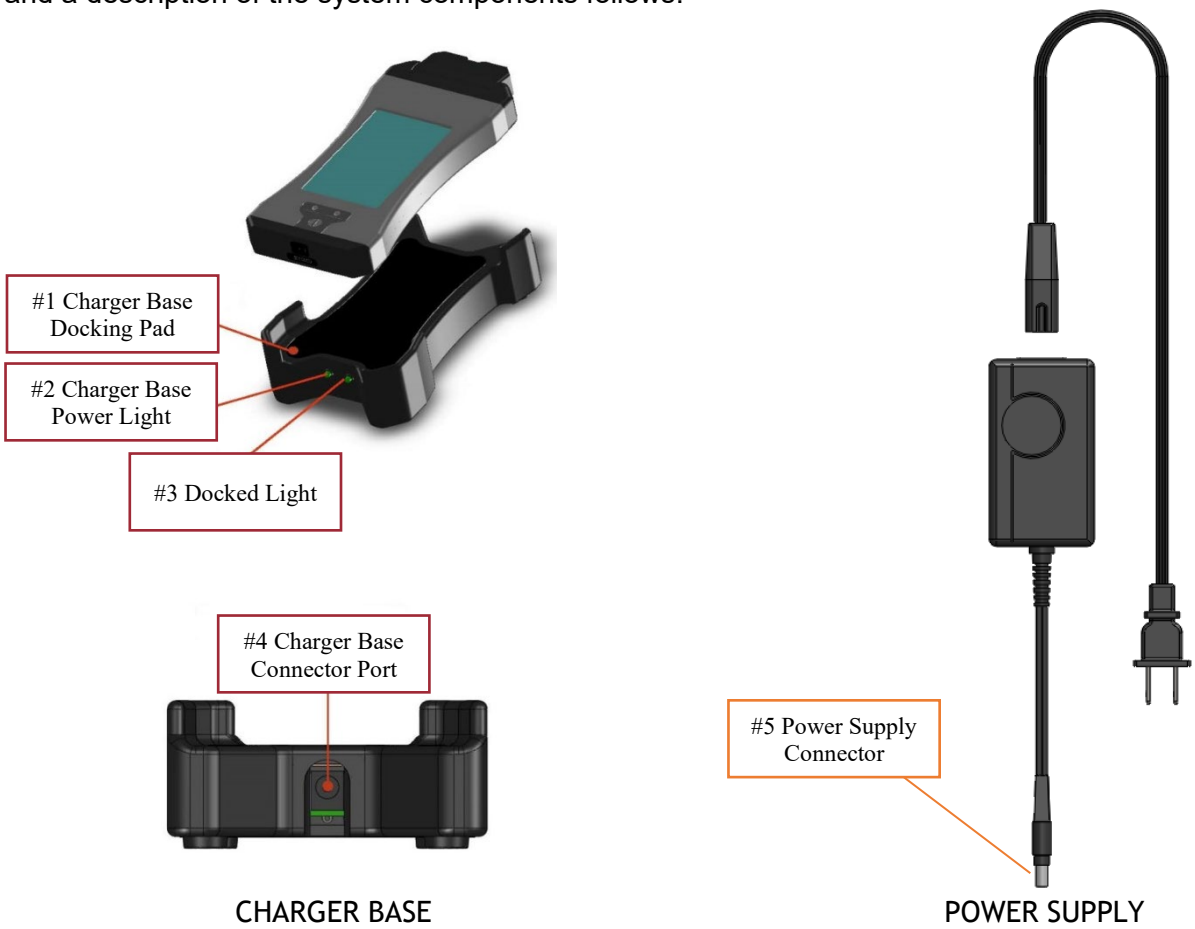


Figure 2: The Erchonia HLS Laser Charger Base and Power Supply

#1 CHARGER BASE DOCKING PAD

The Charger Base Docking Pad is a custom based system specifically designed to charge the laser device. It is an inductive charging system that charges the device wirelessly.

#2 CHARGER BASE POWER LIGHT

The Charger Base Power Light is an LED power indicator that will light up when the Power Supply connector is plugged into the Charger Base Docking Pad.

#3 DOCKED LIGHT

The Docked light is an LED indicator light that will light up to indicate when the device is correctly docked in the charger base docking pad. The LED will flash ON and OFF when correctly in place and turn off when removed from the charger base docking pad.

#4 CHARGER BASE CONNECTOR PORT

The Charger Base Connector Port is the location where the Power Supply Connector is plugged into for charging.

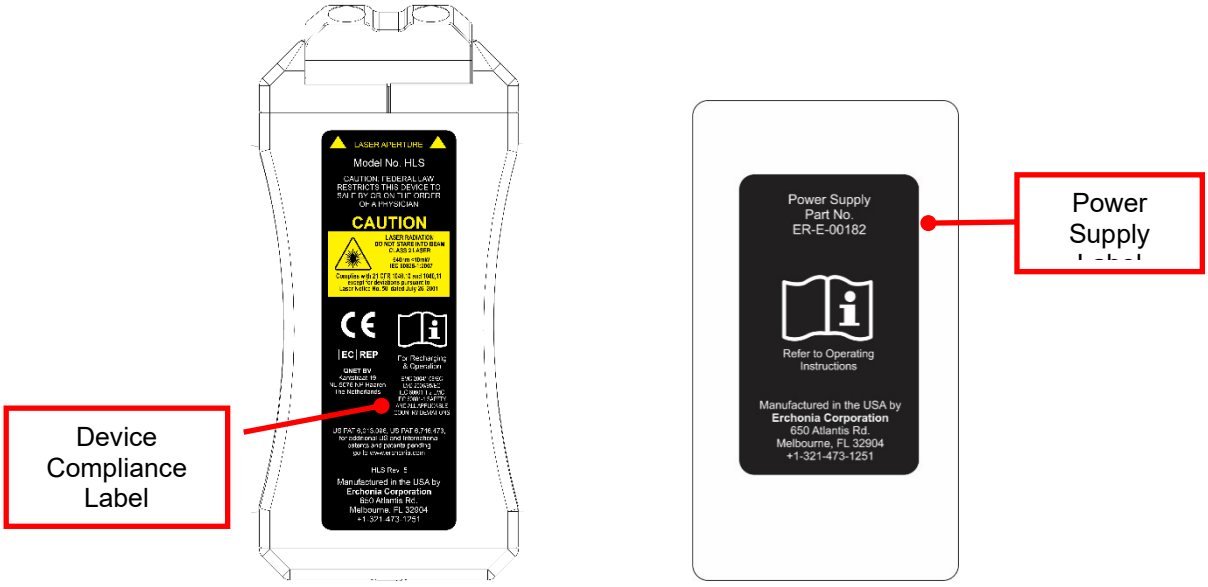
#5 POWER SUPPLY CONNECTOR

The Power Supply Connector plugs into the Inductive Charger Base Connector Port to provide power to charger base.

DEVICE LABELING

The Erchonia HLS 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.



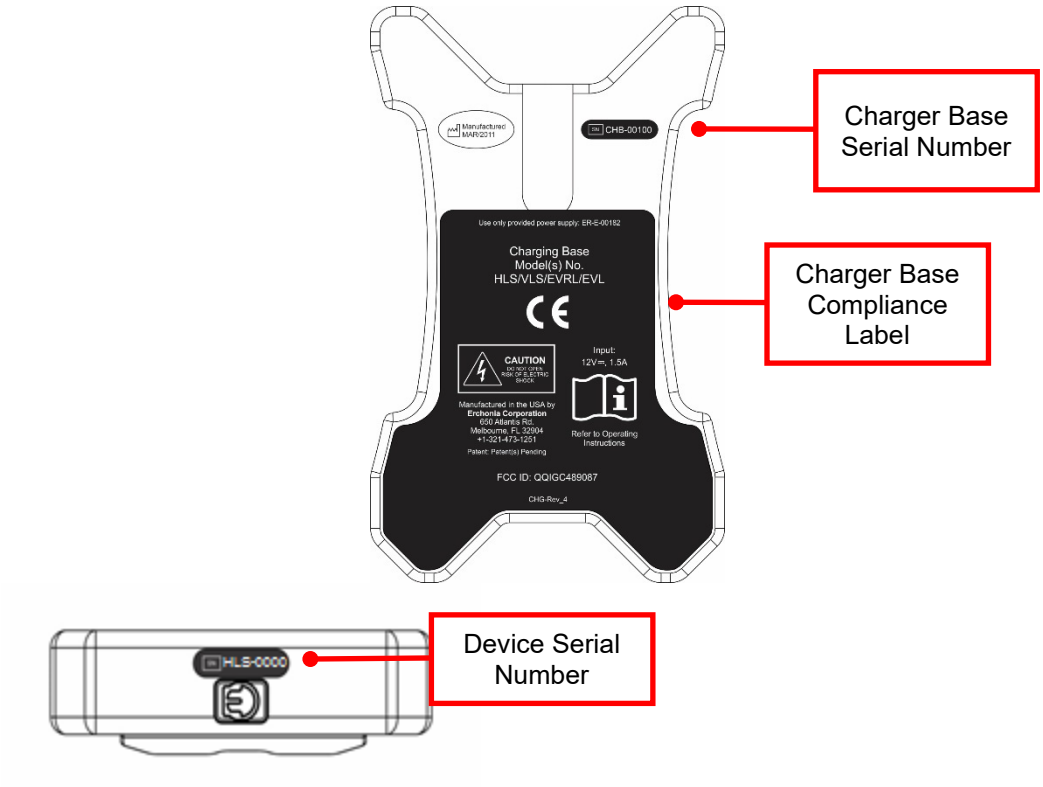


Figure 3: Erchonia HLS Laser **L**abeling

DEVICE SAFETY

RISK AND PREVENTION OF EYE INJURY

The Erchonia® HLS Laser Device 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 patient. A Class 2 laser is determined to have a chronic viewing hazard. Pointing the laser beam directly into the eye and maintaining it there for an extended period of time could prove to be damaging.

To ensure there is no possible instance of residual effect, eye protection will be implemented for both the investigator administering the in-office study procedures with the Erchonia® HLS and for the subject receiving the laser procedure administrations.

Treatment Administration Investigator Safety Glasses

The Treatment Administration Investigator safety glasses sufficiently and effectively block the laser light spectrum at OD 2+ @ 640nm, OD 0.75 @ 405nm VLT60 and are shown in Figure 4 below.

Figure 4: Treatment Administration Investigator Safety Glasses

Subject Safety Goggles

For the subject receiving the procedures with the Erchonia® HLS Laser Device, a pair of specialty safety goggles is provided for use during all in-office procedure applications. These safety glasses are KenTek Corporation KenTek KGOG Medium Goggles Filter#6101 light blue safety goggles. These safety goggles are completely enclosing of the eyes and surrounding area such that no light may permeate the sHLS to reach the eye. The KenTek KGOG Medium Goggles Filter#6101 has the following specifications:

- *Filter#6101 specifications:*
  - ✓ OD 2.30 @ 635nm
  - ✓ VLT 60%
  - ✓ 635D LB2
  - ✓ KTK CE 2056

- *Frame specifications*
  - ✓ Goggle fit-over with foam comfort pads and elastic strap
  - ✓ Curved lens
  - ✓ IdHLS for smaller faces and Rx lenses
  - ✓ *Size:* Medium Fit-Over
  - ✓ *Dimensions***:** Lens: Width 63mm, Height 40mm; Bridge: 18mm ; Inside Front: 153mm

The KenTek Corporation KenTek KGOG Medium Goggles safety goggles are shown in Figure 5 below.

Figure 5: KenTek Corporation KenTek KGOG Medium Goggles Safety Goggles

COMPLIANCE APPLICABLE CODES

The Erchonia HLS is compliant with the following applicable codes:

FDA
21CFR 820 – Quality System Regulations
21CFR 1040.10 and 1040.11 by laser Notice 50

ISO
13485 – Medical Device Quality
14971 – Risk Management

EMC 2004/108/EC
LVD 2006/95/EC
IEC 60601-1-2 EMC
IEC 60601-1- Safety

IEC 60825-1 – Laser Safety
CB Certified

FDA DETERMINATION OF NON-SIGNIFICANT RISK (NSR) STATUS

The FDA has determined the Erchonia® HLS Laser device (technically identical to the Erchonia® EML Laser) to be non-significant risk (NSR) through the following 510(k) clearances:

1. 510(k)#: K072206
Device Name: Erchonia® EML Laser
Indications for Use: For the temporary reduction in post-surgery pain at 24 hours after surgery following bilateral breast augmentation surgery.

2. 510(k)#: K041139
Device Name: Erchonia® EML Laser
Indications for Use: The Erchonia EML is indicated as an adjunct to liposuction procedures of the thighs, hips and stomach for reduction of pain associated with the recovery process.

IRB DETERMINATION OF NON-SIGNIFICANT RISK (NSR) STATUS

Independent Review Consulting, Inc.'s/Ethical and Independent Review Services' Institutional Review Board determined the Erchonia® HLS (aka EML) laser device to be a non-significant risk (NSR) device when applied in the following studies that supported the above-referenced FDA 510(k) clearances:

1. **IRC# 05122, NSR# DER-001:** Erchonia® EML Breast Implant Clinical Study; Version 2, 08/10/05.

2. **IRC# 02093, NSR# DTU-003:** Erchonia® EML Liposuction Clinical Study; Version 2. 08/12/2003.

PLACEBO DEVICE INFORMATION

The placebo (fake) Erchonia® HLS to be employed in this pivotal trial is designed to have the same physical appearance as the actual Erchonia® HLS, including the appearance of any visible light output. The placebo laser device will therefore emit light when activated that is indistinguishable to both the subject and to the investigator. As the laser light does not put out any notable degree of heat or noise, these are not distinguishing factors for subjects or investigators between the active and placebo treatment groups.

The design of the placebo device to be employed in this pivotal trial is identical to that employed in numerous prior feasibility and pivotal clinical trials employing Erchonia Corporation low level laser devices. In each of those prior studies, the lack of effectiveness of the placebo device on the target indication was clearly established. The results from several of these placebo-controlled pivotal studies conducted to evaluate efficacy of the actual Erchonia laser device over a placebo device, with the placebo device configured in the manner described and intended in the current pivotal trial, were used to support 510(k) submissions to the Food and Drug Administration (FDA) that resulted in clearances being granted for various indications. In each of these pivotal trials, the active device comprised red light laser diodes as in the current study, with the placebo device designed to emit the same visible light output without therapeutic effect.

Application of the same placebo device design and configuration in numerous prior pivotal trials whose results demonstrated statistical significance of application of the active laser device over a placebo device and resulted in FDA clearances establishes the lack of effectiveness of the placebo device with respect to the placebo device design intended for application in the current pivotal trial.

Please find below a listing of each of the FDA 510(k) clearances pertaining to the family of Erchonia® red diode laser devices:

- **510(k)#:** K121695 & K082609
Erchonia® ML Scanner (MLS) & Erchonia® Zerona: 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.

- **510(k)#:** K121690 & K120257
Erchonia® ® MLS, Zerona, Zerona-AD: 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.
- **510(k)#:** K101430
Erchonia® MLS-AC Derma Scanner™: indicated while using the red diodes for adjunctive use in providing temporary relief of minor chronic neck and shoulder pain of musculoskeletal origin, and while using the blue diode, to treat moderate inflammatory Acne Vulgaris.

- **510(k)#:** K072206
Erchonia® EML Laser: indicated for the temporary reduction in post-surgery pain at 24 hours after surgery following bilateral breast augmentation surgery.

- **510(k)#:** K050672

Erchonia® EVRL Laser: 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.

- **510(k)#:** K041139

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

- **510(k)#:** K100509

Erchonia® THL1 Laser: indicated for use in providing temporary relief of minor chronic neck and shoulder pain of musculoskeletal origin.

STUDY INDICATION AND RATIONALE; THEORY OF MECHANISM OF OPERATION; & SUPPORTIVE CLINICAL DATA

STUDY INDICATION: AUTISTIC DISORDER

Autism spectrum disorder (ASD) is a range of complex neurodevelopment disorders characterized by social impairments, communication difficulties, and restricted, repetitive, and stereotyped patterns of behavior. Autistic disorder, sometimes called autism or classical ASD, is the most severe form of ASD, while other conditions along the spectrum include a milder form known as Asperger syndrome, and childhood disintegrative disorder and pervasive developmental disorder not otherwise specified (PDD-NOS).

Although ASD varies significantly in character and severity, it occurs in all ethnic and socioeconomic groups and affects every age group, with symptoms appearing before age 3. The Centers for Disease Control (CDC): Morbidity and Mortality Weekly Report, March 30, 2012 estimates that 1 out of 88 children age 8 will have an ASD, with males four times more likely to have an ASD than females.

Common Signs and Symptoms

The primary sign of ASD is impaired social interaction. As early as infancy, a baby with ASD may be unresponsive to people or focus intently on one item to the exclusion of others for long periods of time. A child with ASD may appear to develop normally and then withdraw and become indifferent to social engagement.

Children with an ASD may fail to respond to their names and often avoid eye contact with others. They have difficulty interpreting what others are thinking or feeling because they can't understand social cues, such as tone of voice or facial expressions, and they don't watch other people's faces for clues about appropriate behavior. They also lack empathy.

Many children with an ASD engage in repetitive movements such as rocking and twirling, or in self-abusive behavior such as biting or head-banging. They also tend to start speaking later than other children and may refer to themselves by name instead of "I" or "me." Children with an ASD don't know how to play interactively with other children. Some speak in a sing-song voice about a narrow range of favorite topics, with little regard for the interests of the person to whom they are speaking.

Children with characteristics of an ASD may have co-occurring conditions, including Fragile X syndrome (which causes mental retardation), tuberous sclerosis, epileptic seizures, Tourette syndrome, learning disabilities, and attention deficit disorder. About 20-30% of children with an ASD develop epilepsy by the time they reach adulthood.

Etiology

The cause of ASD is not clearly understood, but it is believed that both genetics and environment likely play a role. Several genes associated with the disorder have been identified. Studies of people with ASD have found irregularities in several regions of the brain.

Other studies suggest people with ASD have abnormal levels of serotonin or other neurotransmitters in the brain, suggesting that ASD could result from the disruption of normal brain development early in fetal development caused by defects in genes that

control brain growth and that regulate how brain cells communicate with each other, possibly due to the influence of environmental factors on gene function.

Twin and family studies strongly suggest that some people have a genetic predisposition to autism. Identical twin studies show that if one twin is affected, there is up to a 90% chance the other twin will be affected. In families with one child with ASD, the risk of having a second child with the disorder is approximately 5%, which is greater than the risk for the general population. In some cases, parents and other relatives of a child with ASD show mild impairments in social and communicative skills or engage in repetitive behaviors. Evidence also suggests that some emotional disorders, such as bipolar disorder, occur more frequently than average in the families of people with ASD.

Diagnosis

ASD varies widely in severity and symptoms and may go unrecognized, especially in mildly affected children or when it is masked by more debilitating handicaps. Very early indicators that require evaluation include:

- no babbling or pointing by age 1
- no single words by 16 months or two-word phrases by age 2
- no response to name
- loss of language or social skills
- poor eye contact
- excessive lining up of toys or objects
- no smiling or social responsiveness.

Later indicators include:

- impaired ability to make friends with peers
- impaired ability to initiate or sustain a conversation with others
- absence or impairment of imaginative and social play
- stereotyped, repetitive, or unusual use of language
- restricted patterns of interest that are abnormal in intensity or focus
- preoccupation with certain objects or subjects
- inflexible adherence to specific routines or rituals.

Often a questionnaire or other screening instrument is used to gather information about a child's development and behavior. Some screening instruments rely solely on parent and/or other caregiver(s) observations, while others rely on a combination of parent/caregiver and doctor observations. If screening instruments indicate the possibility of an ASD, a more comprehensive evaluation is usually indicated.

A comprehensive evaluation requires a multidisciplinary team, including a psychologist, neurologist, psychiatrist, speech therapist, and other professionals who diagnose children with ASDs. The team members will conduct a thorough neurological assessment, hearing assessment and in-depth cognitive and language testing.

Children with some symptoms of an ASD but not enough to be diagnosed with classical autism are often diagnosed with PDD-NOS. Children with autistic behaviors but well-developed language skills are often diagnosed with Asperger syndrome. Much rarer are children who may be diagnosed with childhood disintegrative disorder, in which they develop normally and then suddenly deteriorate between the ages of 3 to 10 years and show marked autistic behaviors.

Currently Available Treatments

There is no cure and no single best treatment for individuals with autistic disorder. The current standard treatment approach is to customize an individual highly structured, specialized program or treatment plan incorporating therapies and behavioral interventions targeted toward improving the individual's specific symptoms of autism. Early identification and intervention, the earlier the possible, is also optimal for maximizing positive outcomes and symptom management.

A team approach is generally employed, involving the collaboration of the child's parents and/or other caregivers, the treating physician and/or other healthcare professionals such as physical therapists, occupational therapists, and also school staff.

Components of the treatment plan may include one or all of the following, as applicable to the individual child's needs:

- *Therapies*: Several treatment approaches have been identified. Therapists use highly structured and intensive skill-oriented training sessions to help children develop social and language skills, such as Applied Behavioral Analysis.Some approaches focus on developing skills and learning appropriate behaviors. Other approaches are reward-based using positive reinforcement to encourage children to practice certain skills.

- *Dietary interventions* have been helpful for some children.

- *Educational/behavioral interventions*: Family counseling for the parents and siblings of children with an ASD often helps families cope with the challenges of living with a child with an ASD.

- *Medications:* There is currently no FDA approved treatment for the core symptoms of autism, but risperidone (Risperdal®) and aripiprazole (Abilify®) have FDA approval for disruptive behaviors associated with autism:

  - ✓ Risperdal® is a prescription medication indicated for the treatment of irritability associated with autistic disorder in children and adolescents aged 5-16 years, including symptoms of aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods.

  - ✓ Abilify® is a prescription medication indicated for the treatment of irritability associated with Autistic Disorder in pediatric patients 6 to 17 years of age

Some physicians may also prescribe medications for the treatment of other specific autism-related symptoms, such as anxiety, depression, or obsessive-compulsive disorder.

Antipsychotic medications are used to treat severe behavioral problems.

Seizures can be treated with one or more anticonvulsant drugs. Medication used to treat people with attention deficit disorder can be used effectively to help decrease impulsivity and hyperactivity

THEORY OF MECHANISM OF OPERATION

Autism is a complex neurodevelopmental condition that is diagnosed based on three fundamental behavioral domains: aberrant social and communication interactions and specific behavioral patterns. Furthermore, symptom manifestation is variable among suffers, ranging from a non-verbal child with mental retardation to high-functioning adults. Behavior patterns include hyperactivity, irritability, communication language deficits, and intellectual impairment. The majority of diagnosed cases of autism are idiopathic with an enigmatic pathogenesis, and as a result, therapeutic approaches have focused on mitigating specific symptoms rather than treating disease etiologies.

Therapeutic limitations derive from the disease's heterogeneity, which offers no lucid approach. Nevertheless, commonalities have emerged following extensive neuroimaging investigations. Magnetic resonance imaging (MRI) studies have demonstrated increased brain volume and head circumference during early developmental childhood, with the greatest pronouncement in infants and toddlers. This finding suggests that autistic brains experience a period a rapid overgrowth which hampers further development during later developmental stages. Morphological aberrations have been observed in the hippocampus, anterior cingulate cortex, prefrontal cortex, amygdala, and cerebellum. Another consistent observation has also been the reduction in cerebellar vermis volume, which helps to explain specific behavioral patterns in children.

Molecular analysis of postmortem brain tissue has revealed reduced Purkinje cell numbers, which helps to explain aberrant locomotive activity and level presser function. Another finding has been impaired neuronal connectivity within the cerebellum, amygdala, anterior cingulate cortex, and dorsolateral prefrontal cortex. Consequently, synapse structure and function has demonstrated impairment in postmortem evaluations. Dendritic spines of glutamatergic neurons in autistic patients have shown morphological alterations and suppressed density, which, in turn, results in diminished synaptic transmissions. Nascent spines have been reported in frontal, temporal, and parietal cortices of autistic patients, and have a negative correlation with cognitive abilities in autism. Other neurological aberrations include signaling through metabotropic glutamate receptor (mGluR) and γ-aminobutyric acid (GABA)ergic system.

Studies have reported reduced frontal lobe GABA levels in children with autism. Although the genetic association of autism remains complex and elusive, specific genetic categories related to synaptogenesis, guanine nucleotide triphosphate (GTP) cascades, axon guidance, and neuron motility, and immune-associated genes have been formed. Concerning the immune system, elevated levels of chemokines and pro-inflammatory cytokines have been observed in brain tissue. Specifically, interleukin-6 (IL-6) has been found elevated and responsible for the overexpression of granule cells. Furthermore, formation of excitatory synapse and not inhibitory synapses were observed, which indicates IL-6 may hamper cell adhesion and neuronal migration. The production of pro-inflammatory cytokines may also be secondary to microglial activation, inducing the formation of glial scars, pro-inflammatory cytokines, and deleterious levels of reactive oxygen species. Promising data have shown improvements in symptoms following administration f anti-inflammatory drugs. Interestingly, recent data have shown the role GABA systems play in downregulating inflammation in the brain, and with suppressed levels of GABA reported in autistic patients, it has been proposed that GABA depression and immune activation could be strongly related.

The elusive and byzantine pathophysiology of autism engenders a marked challenge for health care providers; nevertheless, one technology that has demonstrated auspicious outcomes is low-level laser therapy (LLLT). Operating under the auspices of photochemistry, LLLT uses photonic energy to modulate the behavior and function of cells; this is accomplished by stimulating molecular entities capable of absorbing discrete wavelengths. For instance, cytochrome c oxidase (CCO), a terminal enzyme of the respiratory change, contains a tetrapyrrole prosthetic group that has been shown to absorb 635nm. Photon-induced activation of CCO increases cell bioenergetics, which, in turn, activates intra-cellular secondary signaling cascades that in turn affect growth factor synthesis, cell proliferation, cytokine production, and expression of specific transcription factors. Studies have reported increased adenosine triphosphate (ATP) synthesis along with activation of the intracellular redox state following the production of reactive oxygen species (ROS). As an essential bio-catalyst, ATP lowers the activation for pivotal biochemical reactions within cells. Concerning neurons, laser irradiation has been shown to promote the recovery of injured peripheral nerves and the spinal cord. Moreover, studies have revealed that excitable cells like neurons can be directly stimulated by light, enhancing the action potential of the cell increasing the release of neurotransmitters such as glutamate and acetylcholine.

Influence of the intracellular redox state enables LLLT to affect two well defined transcription factors, NF-κB and activator protein-1 (AP-1). The laser induced shift towards a more oxidized (alkalized) state impacts redox-sensitive transcription factors and subsequent gene expression. Recent evidence indicates that laser therapy can significantly diminish the expression of COX-2 by affecting the regulatory system controlling NF-κB, resulting in the reduction of inflammation. By suppressing the mechanism that upregulates inflammation, the application of laser irradiation can serve as a non-invasive means to down-regulate inflammatory agents reducing the severity of acne perhaps even preventing its onset.

Preliminary studies have shown, subsequent to LLLT, upregulation of cell bioenergetics and sequential influence on intra-cellular secondary cascades. Clinical outcomes include nerve regeneration, increased neurotransmitter release, growth factor synthesis, and neo-vascularization to name a few. Accordingly, auspicious positioning of laser along impaired regions of an autistic brain could elicit a positive therapeutic outcome.

The following articles provide additional support for the proposed theory of mechanism of operation of laser therapy to improving the symptoms of autism.

1. **Photobiomodulation and the brain: a new paradigm**
   Madison Hennessy1 and Michael R Hamblin2,3,4
   J Opt. 2017 January; 19(1): 013003

2. **The Nuts and Bolts of Low-level Laser (Light) Therapy**
   Hoon Chung1,2, Tianhong Dai1,2, Sulbha K. Sharma1, Ying-Ying Huang1,2,3, James D. Carroll4, and Michael R. Hamblin1,2,5
   Ann Biomed Eng. 2012 February; 40(2): 516–533.

3. **Laser Acupuncture for Autism Spectrum Disorder a Randomized Sham Controlled Trial**
   Dr. Shahzad Anwar, Prof. Dr. Malik Muhammad Nazir Khan, Dr. Faiza Munir Qazi

SUPPORTIVE CLINICAL DATA

1. ERCHONIA® HLS FEASIBILITY PROOF OF CONCEPT TRIAL

September 2012

BACKGROUND: The purpose of this feasibility study was to demonstrate preliminary efficacy of the Erchonia® HLS laser device, manufactured by Erchonia Corporation (the Sponsor), for the treatment of symptoms associated with autistic disorder in children prior to designing and executing a full-scale pivotal trial to the same effect.

STUDY DESIGN: The study was an open-label single group design wherein all study subjects received the active study treatment with the Erchonia® HLS.

SUBJECTS: Eleven (9 male and 2 female) children and adolescents aged from 5 years 4 months to 16 years 10 months with autistic disorder who satisfied the study qualification criteria were enrolled in the study. Each subject had a current diagnosis of autistic disorder as per the DSM-IV-TR criteria and confirmed by the ADI-R, with a CGI-S score or 4 or greater, as well as demonstrated 'irritable' behaviors with an ABC Irritability Subscale score of 18 or greater.

STUDY PROCEDURE: The Aberrant Behavior Checklist (ABC) assessment tool was administered at Baseline evaluation (before receiving the first laser treatment administration) and at study Endpoint evaluation (after completion of the entire laser treatment administration protocol).

RESULTS: The complete results analysis for the ABC assessment tool, for each individual Subscale score and the Global score are presented below. Subscale I: Irritability/Agitation was the primary efficacy outcome measure of interest.

(i) ABC Subscale and Global Scores

Table 1 below shows the mean and standard deviation of the Baseline (pre-treatment) and Endpoint (after the final treatment administration) scores and the change that occurred across the two measures for each of the 5 ABC Subscale Scores and the Global Score.

Table 1: Mean, Standard Deviation and Change of Baseline and Endpoint ABC Subscale and Global Scores

	Baseline (n=11)		Endpoint (n=11)		Change (n=11)	
	Mean	**St. Dev.**	**Mean**	**St. Dev.**	**Mean**	**St. Dev.**
Subscale I: Irritability/Agitation	14.45	8.18	5.36	6.70	-9.09	6.76
Subscale II: Lethargy/Social Withdrawal	11.36	7.16	4.00	4.31	-7.36	5.64

Subscale III: Stereotypic Behavior	7.36	5.20	3.64	3.23	-3.73	3.55
Subscale IV: Hyperactivity & Noncompliance	18.00	11.93	6.91	6.20	-11.09	9.40
Subscale V: Inappropriate Speech	6.18	3.37	2.73	1.35	-3.45	2.46
Global Score	***57.36***	***31.56***	***22.64***	***19.22***	***-34.73***	***25.84***

A series of t-tests for 2 correlated samples was conducted to evaluate the significance of the change in Baseline to Endpoint ABC Subscale and Global scores. The Baseline to Endpoint changes were found to be statistically significant for all 5 subscale scores and for the Global Score of the ABC, as shown in Table 2 below.

Table 2: T-test Results for Baseline to Endpoint Changes in ABC Subscale and Global Scores

	μa-μb	t	df	p(two-tailed)	p
Subscale I: Irritability/Agitation	9.09	+4.46	10	0.0012	p<0.005
Subscale II: Lethargy/Social Withdrawal	7.36	+4.33	10	0.0015	p<0.005
Subscale III: Stereotypic Behavior	3.73	+3.48	10	0.006	p<0.01
Subscale IV: Hyperactivity & Noncompliance	11.09	+3.91	10	0.003	p<0.005
Subscale V: Inappropriate Speech	3.45	+4.65	10	0.00091	p<0.001
Global Score	***34.73***	***+4.46***	***10***	***0.0012***	***p<0.005***

ADVERSE EVENTS: there were no adverse events reported or observed for any of the 11 subjects throughout the duration of the pilot study, and no subject showed any negative score changes from Baseline to Endpoint.

CONCLUSION: For the 11 subjects in this feasibility study, there was a sizeable and statistically significant decrease in mean scores for all 5 Subscale scores and for the Global Score on the ABC following completion of the treatment administration protocol with the Erchonia® HLS Laser Device, indicative of improvement in the overall symptoms and behaviors associated with Autistic Disorder. Therefore, the results of this feasibility study indicate that low level laser therapy may be effective in improving the symptoms and behaviors of autistic disorder in children and adolescents.

2. **A double-blind, placebo-controlled randomized evaluation of the effect of the Erchonia® HLS laser device on children and adolescents with autistic disorder:** *Version 2.0, January 31, 2013*

BACKGROUND: The purpose of this clinical study was to demonstrate the efficacy of the Erchonia® HLS laser device, manufactured by Erchonia Corporation (the Sponsor), for the treatment of symptoms associated with autistic disorder in children and adolescents aged five (5) to seventeen (17) years, inclusive. This clinical study protocol and results outcome are the result of pre-IDE submission Q130138 and de novo

submission DEN180046 as explained in the 'Regulatory History' section on page 3 above.

STUDY DESIGN: The study was a placebo-controlled, randomized, double-blind design.

SUBJECTS: Forty (40) subjects completed the study, 21 of whom were randomized to the active procedure group and 19 of whom were randomized to the placebo group. The 19 placebo group subjects subsequently participated in a cross-over procedure study option. Subjects were male or female children and adolescents aged 5 to 17 years with a current diagnosis of autistic disorder as per the DSM-V criteria and confirmed by the ADI-R, with a CGI-S score or 4 or greater, as well as demonstrated 'irritable' behaviors with an ABC Irritability Subscale score of 18 or greater. Average subject age was 8.3 years, and three-quarters (75%) of subjects were male.
STUDY PROCEDURE: Subjects received eight 5-minute procedure administrations to the base of the brain and temporal areas with the Erchonia® HLS Laser (active or sham) across a four-week period: two procedures per week, each procedure three to four days apart.

STUDY EVALUATIONS: All subjects were evaluated using the Aberrant Behavior Checklist (ABC) Global Scale and 5 Subscales (Irritability/Agitation, Lethargy/Social Withdrawal; Stereotypic Behavior; Hyperactivity/ Noncompliance and Inappropriate Speech); and the Clinical Global Impressions Severity of Illness (CGI-S) and Improvement/Change (CGI-C) scales at baseline, week 2 (interim), week 4(endpoint) and week 8 (post-procedure) of the study. Test group subjects were additionally evaluated at 6 months post-procedure.

STUDY RESULTS

Primary Outcome Measure: Primary outcome measure was predefined as the mean change from baseline to endpoint in the Aberrant Behavior Checklist (ABC) Irritability & Agitation Subscale score. Primary efficacy study success was pre-established as the detection of a minimum mean difference of -8.5 points between test and placebo groups in the baseline to endpoint change in ABC Irritability Subscale score adjusted for baseline ABC Irritability Subscale score.

The adjusted mean difference in the baseline to study endpoint change in the ABC Irritability Subscale score between all 40 active procedure subjects and placebo subjects was -13.82 in favor of the active procedure group, notably greater than the pre-established study success criteria of a -8.5-point difference. ANCOVA analysis found this difference to be statistically significant at $p<0.0001$ ($F=30.07$), independent of baseline ABC Irritability Subscale score.

ABC Irritability	**Combined (n=401)**		**Test (n=21)**		**Cross-Over (n=19)**		**Placebo (n=19)**	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Baseline	30.45	6.74	30.52	6.73	30.37	6.94	29.58	6.83
Endpoint	16.90	9.05	15.71	9.94	18.21	8.02	29.89	6.55

Change	*-13.55*	*6.387*	*-14.81*	*6.40*	*-12.16*	*6.21*	*0.32*	*1.38*

The table below show the mean and standard deviation and the magnitude of change in ABC Irritability Subscale scores from baseline to endpoint.

Positive Responder Rate: *Positive Response Rate* was defined as satisfaction of both of the following 2 criteria:

- ≥ 25% reduction from baseline to endpoint in the ABC Irritability Subscale score; AND
- CGI-I scale rating of 1 (very much improved) or 2 (much improved) at study endpoint

Eighty per cent (80%) of all 40 active procedure group subjects met the Positive Responder Rate compared with no (0%) placebo group subjects. Chi Square analysis found the differences between each of the 3 active procedure groups and the placebo group to be statistically significant, at $p<0.0001$.

ABC Global and Subscale Scores Across Study Duration: Mean change in each of the ABC Global Score and 5 Subscale Sores across study duration between procedure groups was evaluated through ANOVA analysis. Mean changes in scores for test group subjects decreased progressively and sizably across study duration including during a 4-week follow-up period during which time no procedures were administered, with the changes found to be statistically significant for each of the 3 active procedure groups ($p<0.0001$). Conversely, all scores were essentially unchanged across study duration for placebo group subjects and not statistically significant, at $p>0.05$.

CGI-S Scores: Change in CGI-S scores across study duration between procedure groups was evaluated. At baseline, all subjects (100%) in both procedure groups were rated in the top 3 severity of condition ratings of '5: Marked', '6: Severe' or '7: Amongst the most extreme of all patients with this condition'. CGI-S scores improved progressively and substantially across study duration for each of the 3 active procedure group subjects but not for placebo group subjects. By Week 8, all placebo group subjects (100%) retained a 5-7 CGI-S rating while only 35% of all 40 active procedure subjects retained a 5-7 CGS-S rating.

CGI-C Scores: Change in CGI-C scores across study duration between procedure groups was evaluated. CGI-C ratings for each of the 3 active procedure group subjects demonstrated continuous progressive improvement in symptom presentation across study duration. By Week 8, the presentation of symptoms and behaviors of autistic disorder for 85% of all 40 active procedure group subjects were reported as being 'Very Much Improved' or 'Much Improved' Conversely, there was essentially no change in CGI-C ratings across study duration for placebo group subjects.

6 Month Long-Term Follow-Up Evaluation: All 19 subjects originally randomized to the placebo subject group completed an additional 6-month post-procedure evaluation. Each of the outcome measures continued to demonstrate meaningful progressive improvement.

Adverse Events: No adverse event was reported for or by any subject throughout study duration.

CONCLUSION: The Erchonia® HLS Laser is an effective tool for improving irritability and the presentation of other symptoms and behaviors associated with autistic disorder in children and adolescents, with positive changes maintained and augmented over time, including a six-month follow-up period during which time no procedure administration occurred.

STUDY RATIONALE

Considering the positive outcomes of the prior feasibility and clinical studies, it is determined that application of the Erchonia® HLS may provide a simple, non-invasive, safe, effective and side-effect free alternative therapy to reduce the severity of irritability symptoms and behaviors of autistic disorder in children. The currently proposed full-scale controlled pivotal trial is intended to demonstrate this to a statistically significant and clinically meaningful extent.

STUDY DESIGN

This clinical study is a double-blind, placebo-controlled randomized parallel group design.

TREATMENT GROUPS

Each subject is randomized to the test treatment group or to the placebo treatment group, as follows:

- Test Group: Subjects randomized to the test group will receive the study treatments with the active (true) Erchonia® HLS device.
- Placebo Group: Subjects randomized to the placebo group will receive the study treatments with the 'fake' (placebo) Erchonia® HLS device.

DOUBLE BLIND DESIGN

This clinical study will be a double-blind design, such that neither the subject nor the investigator will be aware of whether a subject has been assigned to the test group or to the control group until after the study is complete.

Maintenance of study double-blind throughout the study duration will be achieved as follows:

1) Each subject will be randomly assigned to Treatment Group A or to Treatment Group B. Subjects assigned to Treatment Group A will be treated with the Erchonia® HLS A and subjects assigned to Treatment Group B will be treated with Erchonia® HLS B. Only the study Sponsor will know which label ('A' or 'B') corresponds to the actual (test) HLS device and which label corresponds to the 'fake' device until the final study data analysis is complete. The Sponsor will ensure that this information is stored and maintained confidentially at the Sponsor's work site. This knowledge will not be shared with the investigators, the subjects, or the study Monitor until the final data analysis is complete.

2) The fake (placebo) Erchonia® HLS is designed to have the same physical appearance as the actual Erchonia® HLS, including the appearance of any visible light output, and neither the active nor the placebo lasers put out any notable degree of heat or noise. Therefore, there are no distinguishing factors between the active and placebo lasers for subjects or investigators. Additional information on the design, application and proven ineffectiveness of the placebo HLS Laser Device to be used in this study is contained above on pages 10-11 of this protocol document under the section titled: PLACEBO DEVICE INFORMATION.

3) There will be two independent investigators interacting with subjects: (i) *administration investigator*: who will be responsible for administrating the study treatments; (ii) *assessment investigator*: who will be responsible for recording the study outcome measures. Only the administration investigator will be aware of whether a subject is assigned to Treatment Group A or B, although he or she will not be made aware of whether A or B corresponds to the true or fake laser. Neither the assessment investigator nor the subject will be aware of the subject's A/B Group assignment. In this way, the assessment investigator will not be able to form an association between A/B Treatment Group and active/sham device over the course of the study if a treatment effect is observed.

4) During the laser procedures, both the subject and the administration investigator will wear safety glasses that filter out the laser light spectrum. The administration investigator will wear KenTek Corporation KenTek C22-KMT-6101 light blue safety glasses and the subject will wear KenTek Corporation KGOG-6101 light blue Medium safety goggles. Additional information on this safety eyewear is contained above on pages 6-8 under the section titled: DEVICE SAFETY: RISK AND PREVENTION OF EYE INJURY.

TREATMENT GROUP RANDOMIZATION

Subject allocation to treatment group (A or B) will be via a randomized block design with varying block sizes of two, four and six subjects. In each block, one-half of the subjects will be randomly assigned to Group A and the other half will be randomly assigned to Group B.

Randomization will be attained using computer generation sequence methodology, ensuring that the randomization methodology and the generated allocation sequence is concealed from the investigator and subjects.

Concealment will be insured as follows:

(i) Each computer-generated randomization sequence is unique and will therefore not be able to be replicated.
(ii) Randomization will occur to either 'Group A' or to 'Group B' rather than to a test or placebo group, and only the designated individual at the study Sponsor's site will know which assignment (A or B) corresponds to the active Erchonia® HLS device and which corresponds to the fake device, with this information not to be revealed until study unblinding that occurs after all data has been entered into the database and the database is sealed prior to statistical analyses.

SUBJECTS

Subjects will be those whose caregivers voluntarily sign the informed consent form, who pass the study qualification evaluation and are subsequently enrolled in the study.

<u>Subject Recruitment</u>
The test site will be responsible for recruitment of its own subjects.

The recruitment process will work as follows:

1. A minor individual has a pre-scheduled appointment at the physician's office (that in the context of this clinical study also functions as the investigator's test site) pertaining to his or her ASD and/or related issues.
2. At the time of this visit, if the physician believes that the patient may satisfy the study qualification criteria (i.e. there are no obvious indicators that may exclude him or her), then the physician will present to the patient's caregiver(s) the option of being a subject in the clinical study.
3. If the patient's caregiver expresses interested in possibly having the minor patient take part in the study, the physician – now in the role of study investigator – will personally review the informed consent form with the individual's caregiver(s) and answer any questions. The individual's caregiver may sign the informed consent form at that visit or he or she may think about it for a while and sign the informed consent form at a later time (taking as long as desired, from hours to days to sign as long as study enrollment is continuing at the time the decision to sign is made), or

he or she may refuse to permit the minor child to participate. The Research Subject Information Sheet for Children is also reviewed with the patient, as applicable.
4. Once a caregiver signs the informed consent form, the minor subject will receive a subject ID and proceed to the study qualification evaluation phase of the study.
5. An individual for whom the caregiver decides not to permit participation in the study will continue to work with the physician on the ASD treatment plan goals for the minor patient.

Compensation

A subject or his or her caregiver(s) will not be offered money or any other form of compensation to participate in the clinical study; however, there will also not be any charge for the cost of the study treatments with the Erchonia® HLS laser device or for the cost of any other directly-related evaluations or measurements that occur as part of the subject's participation in this study.

Subject Sample Size

There will be 40 qualified subjects enrolled in this clinical study:

- 20 subjects in the test group
- 20 subjects in the control (placebo) group

Rationale and Justification for Sample Size

This study is powered to compare one active arm with placebo. Sample size calculation is based on the primary efficacy measure of the mean change from study baseline to endpoint (end of the 4-week treatment period) in the Aberrant Behavior Checklist (ABC) Irritability Subscale score adjusted for the baseline ABC Irritability Subscale score.

Based on detecting a mean difference of -8.5 points between test and placebo groups in the change in ABC Irritability Subscale score adjusted for the baseline ABC Irritability Subscale score being considered clinically relevant with a SD of 8.9, a two-sided test with 80% power and a 5% level of significance, the number of subjects needed per treatment group is 18.

From here, it is anticipated that about one-tenth of subjects overall may withdraw or be terminated from the study prior to completion for various reasons. Therefore, the following formula is used to determine the final needed starting sample size for each procedure arm:

Final sample size = sample size X 1/(1-d); where d = # expected dropouts/# subjects enrolled.
Final sample size = 18 X 1/(1-0.11); where d = 2/19
Final sample size = 18 X 1/0.89 = 18 X 1.124 = 20 subjects per treatment group.

Therefore, a minimum starting sample size of 20 subjects in each treatment group (40 subjects in total) is needed to insure that a sufficient number remains at study endpoint (18 evaluable subjects per treatment group) for any significant differences found between treatment groups to be considered statistically valid and representative of the general population being sampled.

A detailed rationale and justification as to why these parameters have been selected and determined as statistically significant and clinically meaningful in this pivotal trial with

respect to determining sample size is contained below in this protocol document on pages 40 through 43, under the section titled: STATISICAL ANALYSIS PLAN.

STUDY PROCEDURE

STUDY TEST BATTERY

The following is information about the diagnostic and assessment tools that will be used in this study. For each tool, the published Spanish translation editions will be utilized, as indicated, as applicable.

DIAGNOSTIC AND ASSESSMENT TOOLS

THE AMERICAN PSYCHIATRIC ASSOCIATION'S DIAGNOSTIC AND STATISTICAL MANUAL, FIFTH EDITION (DSM-5) AUTISM SPECTRUM DISORDER DIAGNOSTIC CRITERIA

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Association; 2013.

A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history (examples are illustrative, not exhaustive, see text):

1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.
2. Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.
3. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.

Specify current severity: Severity is based on social communication impairments and restricted repetitive patterns of behavior (See table below).

B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history (examples are illustrative, not exhaustive; see text):

1. Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases).
2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns or verbal nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat food every day).
3. Highly restricted, fixated interests that are abnormal in intensity or focus (e.g, strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interest).

4. Hyper- or hyporeactivity to sensory input or unusual interests in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).

Specify current severity: Severity is based on social communication impairments and restricted, repetitive patterns of behavior. (See table below.)

C. Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities or may be masked by learned strategies in later life).

D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.

E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level.

Note: Individuals with a well-established DSM-IV diagnosis of autistic disorder, Asperger's disorder, or pervasive developmental disorder not otherwise specified should be given the diagnosis of autism spectrum disorder. Individuals who have marked deficits in social communication, but whose symptoms do not otherwise meet criteria for autism spectrum disorder, should be evaluated for social (pragmatic) communication disorder.

Specify if:
- With or without accompanying intellectual impairment
- With or without accompanying language impairment
- Associated with a known medical or genetic condition or environmental factor
- Associated with another neurodevelopmental, mental, or behavioral disorder
- With catatonia

Table: Severity levels for autism spectrum disorder

Severity level	Social communication	Restricted, repetitive behaviors
Level 3 "Requiring very substantial support"	Severe deficits in verbal and nonverbal social communication skills cause severe impairments in functioning, very limited initiation of social interactions, and minimal response to social overtures from others. For example, a person with few words of intelligible speech who rarely initiates interaction and, when he or she does, makes unusual approaches to meet needs only and responds to only very direct social approaches.	Inflexibility of behavior, extreme difficulty coping with change, or other restricted/ repetitive behaviors markedly interfere with functioning in all spheres. Great distress/ difficulty changing focus or action.
Level 2 "Requiring substantial support"	Marked deficits in verbal and nonverbal social communication skills; social impairments apparent even with supports in place; limited initiation of social interactions; and reduced or abnormal responses to social overtures from others. For example, a person who speaks simple sentences, whose interaction is limited to narrow special interests, and who has markedly odd nonverbal communication.	Inflexibility of behavior, difficulty coping with change, or other restricted/ repetitive behaviors appear frequently enough to be obvious to the casual observer and interfere with functioning in a variety of contexts. Distress and/ or difficulty changing focus or action.
Level 1 "Requiring support"	Without supports in place, deficits in social communication cause noticeable impairments. Difficulty initiating social interactions, and clear examples of atypical or unsuccessful responses to social overtures of others. May	Inflexibility of behavior causes significant interference with functioning in one or more contexts. Difficulty switching between

	appear to have decreased interest in social interactions. For example, a person who is able to speak in full sentences and engages in communication but whose to-and-fro conversation with others fails, and whose attempts to make friends are odd and typically unsuccessful.	activities. Problems of organization and planning hamper independence.

The **Spanish Edition** of the DSM-5 that will be administered in this study is that which is listed on the American Psychological Association (APA) website as endorsed translated publications, with details as follows:

THE AMERICAN PSYCHIATRIC ASSOCIATION (APA) SPANISH EDITION: DSM-5 MANUAL DE DIAGNÓSTICO DIFERENCIAL: DESORDEN DEL ESPECTRO AUTISTA

Spanish Editorial Médica Panamericana
Quintanapalla 8, 4º B
28050 Madrid, Spain
Tel: +34 91 1317810 | Fax: +34 91 4570919
www.medicapanamericana.com

Published Products Available in Spanish:

- Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
- Desk Reference to the Diagnostic Criteria from DSM-5
- The Pocket Guide to the DSM-5 Diagnostic Exam
- DSM-5 Handbook of Differential Diagnosis
- DSM-5 Self-Exam Questions, Test Questions for the Diagnostic Criteria
- DSM-5 Clinical Cases
- DSM-5 Guidebook

US and Canada Distribution
American Psychiatric Publishing
1000 Wilson Blvd. Suite 1825
Arlington, VA 22209
www.appi.org

AUTISM DIAGNOSTIC INTERVIEW, REVISED (ADI-R)

The ADI-R is a comprehensive interview used in research settings to provide a thorough assessment of individuals suspected of having autism or other autism spectrum disorders. The ADI-R has proven highly useful for formal diagnosis as well as treatment and educational planning. It is used to support diagnosis or to determine clinical needs

The ADI-R is composed of 93 items and focuses on three functional domains:

- ✓ Language/Communication
- ✓ Reciprocal Social Interactions
- ✓ Restricted, Repetitive, and Stereotyped Behaviors and Interests

Author(s)/developer(s): Michael Rutter, M.D., FRS, Ann LeCouteur, M.B.B.S., and Catherine Lord, Ph.D.

Population: Individuals suspected of having autism or other autism spectrum disorders, both children and adults, as long as the individual's mental age is above 2 years, 0 months.

Number of items: 93
Administration/Scoring Time: 1 ½- 2 ½ hours
Administration: To administer the ADI-R, an experienced clinical interviewer questions a parent or caretaker who is familiar with the developmental history and current behavior of the individual being evaluated.

Following highly standardized procedures, the interviewer records and codes the informant's responses. Interview questions cover eight content areas:

- ✓ The subject's background, including family, education, previous diagnoses, and medications
- ✓ Overview of the subject's behavior
- ✓ Early development and developmental milestones
- ✓ Language acquisition and loss of language or other skills
- ✓ Current functioning in regard to language and communication
- ✓ Social development and play
- ✓ Interests and behaviors
- ✓ Clinically relevant behaviors, such as aggression, self-injury, and possible epileptic features

Scoring and Interpretation
Because the ADI-R is an interview rather than a test, and because it focuses on behaviors that are rare in non-affected individuals, it provides categorical results rather than scales or norms. Results can be used to support a diagnosis of autism or to determine the clinical needs of various groups in which a high rate of autism spectrum disorders might be expected (e.g., individuals with severe language impairments or certain medical conditions, children with congenital blindness, and youngsters suffering from institutional deprivation). The ADI-R has proven very effective in differentiating autism from other developmental disorders and in assessing syndrome boundaries, identifying new subgroups, and quantifying autistic symptomatology. Extensive use of the ADI-R in the international research community has provided strong evidence of the reliability and validity of its categorical results.

The **Spanish Edition** of the ADI-R that will be administered in this study is the published translation distributed by Western Psychological Services (WPS) Publishing, LLC, as follows:

ADI-R: ENTREVISTA PARA EL DIAGNÓSTICO DEL AUTISMO; EDICIÓN REVISADA
625 Alaska Avenue
Torrance, CA 90503-5124
www.wpspublish.com

ABERRANT BEHAVIOR CHECKLIST (ABC)

The ABC is a 58-item symptom checklist for assessing and classifying problem behaviors of children, adolescents and adults with mental retardation and developmental handicaps at home, in residential and treatment facilities, and community and educational settings. It is also used as an assessment of pharmaceutical and other treatment effects on children, adolescents and adults. The ABC was empirically developed by factor analysis on data from 1,000 individuals.

The 58 items resolve into five subscales:

1. Irritability and Agitation (15 items)
2. Lethargy and Social Withdrawal (16 items)
3. Stereotypic Behavior (7 items)
4. Hyperactivity and Noncompliance (16 items)
5. Inappropriate Speech (4 items)

The Irritability Subscale includes questions about aggression, self-injury, tantrums, agitation and unstable mood on a scale of 0 to 45, with higher scores indicating greater severity. Data from studies of developmentally disabled children indicated that a score of 18 is 1.3 to 1.5 SD above the population means, depending on the age and sex of the child.

Author(s)/developer(s):	Aman, M.G., Sing, N.N., Stewart, A.W., & Field, C.J.
Date of publication:	1985
Population:	Developmentally handicapped children, adolescents and adults aged 5-58.
Number of items:	58
Administration Time:	10-15 minutes
Method of administration:	Teacher or parental observational report; may also be completed by health care practitioners or mental health professionals.
Respondent(s):	Parents, teachers, health care providers, medical/mental health professionals.

Scoring:

- ✓ *Response format:* Each item rated from 0 (not at all a problem) to 3 (the problem is severe in degree).
- ✓ *Scores* for each item are added to obtain subscale and global scores.

Sample norms, reliability, and validity:

- ➢ *Reliability:*

- ✓ *Internal consistency*: Aman et al. reported internal consistencies of 0.86-0.94 in the original development study. Generally, other studies have confirmed this range of internal consistencies.
- ✓ *Test-retest:* The original development study reported test-retest reliabilities of 0.96-0.99.
- ✓ *Inter-rater:* The original development study reported inter-rater reliabilities of 0.17-0.90, with a mean of 0.60. Subsequent studies have found a wide variability of inter-rater reliabilities, ranging from 0.12 to 0.95

➢ *Validity:* There has been extensive validation of the 5-factor structure. The original development study found that the ABC demonstrated moderate discriminative validity with a number of instruments, as well as convergent validity with behavioral observation reports. It also demonstrated adequate predictive validity. Subsequent studies have provided further evidence of predictive, convergent and discriminative validities.

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The **Spanish Edition** of the Aberrant Behavior Checklist (ABC) that will be administered in this study is the published translation distributed by Slosson Educational Publications, Inc, as follows:

Slosson Educational Publications, Inc.
P.O. Box 280
East Aurora, New York 14052, U.S.A
www.slosson.com

CLINICAL GLOBAL IMPRESSIONS (CGI) SCALES

The CGI scales are amongst the most widely used extant brief assessment tools in psychiatry and as assessments in both clinical and research settings.

The CGI is rated on a 7-point scale. The clinician is asked to rate the patient relative to his or her prior experience with other patients with the same diagnosis, with or without collateral information. The CGI is a robust measure of efficacy in many clinical trials and is easy and quick to administer.

CLINICAL GLOBAL IMPRESSIONS SCALE – SEVERITY OF ILLNESS (CGI-S)

The CGI-S is an observer (clinician)-rated scale that measures illness severity.

The physician rates the patient on the CGI-S according to the following question: "Considering your total clinical experience with this patient population, how ill is the patient at this time?"

0 = Not assessed	4 = Moderately ill
1 = Normal, not at all ill	5 = Markedly ill
2 = Borderline ill	6 = Severely ill
3 = Mildly ill	7 = Among the most extremely ill patients

CLINICAL GLOBAL IMPRESSIONS SCALE – GLOBAL IMPROVEMENT (CGI-I)

The CGI-I is an observer (clinician)-rated scale that measures global improvement or change.

The physician rates the patient's condition at each applicable evaluation visit according to how much the patient's condition has changed since baseline evaluation on the following CGI-I scale. The total improvement is rated whether or not, in the physician's judgment, it is due entirely to the study intervention.

0 = Not assessed	4 = No change
1 = Very much improved	5 = Minimally worse
2 = Much improved	6 = Much worse
3 = Minimally improved	7 = Very Much Worse

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The **Spanish Editions** of the CGI-S and CGI-I that will be administered in this study are the published translations for 'Spanish for Mexico' translation as per the National Institute of Mental Health (NIMH), United States Department of Health and Human Services (HHS) and distributed by:

Mapi Research Trust
100 Federal Street
Boston, MA 02108 USA
www.mapi-trust.org

CAREGIVER SATISFACTION WITH STUDY OUTCOME

The subject's caregiver is asked to rate how satisfied he or she is with any change in their child's autism symptoms and behaviors overall following completion of the laser administration procedures with the Erchonia® HLS 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 child's autism symptoms and behaviors overall following the study procedures with the study laser device?"

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

The **Spanish Translation** of the study Caregiver Satisfaction with Study Outcome assessment tool that will be administered in this study will be performed by Language Scientific, Inc. The translated document will be supported by a notarized Certification of Translation

BLINDING EFFICACY EVALUATION TOOLS

Caregiver Perceived Group Allocation and Rationale

The caregiver records whether he or she believes that their child received the study treatment with the true or fake Erchonia® HLS and records verbatim his or her reasoning or rationale for this perceived determination.

Assessment Investigator Perceived Subject Group Allocation and Rationale

The Assessment Investigator records whether he or she believes the subject to have received the study treatment with the true or fake Erchonia® HLS™ and records verbatim his or her reasoning or rationale for this perceived determination.

The **Spanish Translation** of the study Blinding Efficacy Evaluation assessment tools that will be administered in this study will be performed by Language Scientific, Inc. The translated documents will be supported by a notarized Certification of Translation.

STUDY PROCEDURE PROTOCOL

PRE-TREATMENT ACTIVITIES

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's designated caregiver(s) and answer any questions he or she may have. To proceed, the individual's designated caregiver must willingly sign the informed consent form.

ASSIGNMENT OF SUBJECT IDENTIFICATION NUMBER

The subject will be 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."

SUBJECT GROUP RANDOMIZATION

Subjects will be randomly assigned to either Treatment Group A or to Treatment Group B, following the methodology outlined above in the STUDY DESIGN section of the protocol.

STUDY QUALIFICATION EVALUATION: INCLUSION/EXCLUSION CRITERIA

The following tools from the Study Test Battery to be used during Study Qualification Evaluation

- Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V)
- Autism Diagnostic Interview (ADI-R)
- Aberrant Behavior Checklist (ABC) Irritability Subscale
- Clinical Global Impressions – Severity (CGI-S) scale

INCLUSION CRITERIA

- Male or female child or adolescent aged 5 to 12 years
- Subject has met Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V) for autistic disorder within the past 2 years, as diagnosed by a trained, qualified medical professional such as a pediatric neurologist, child psychiatrist or developmental pediatrician
- Diagnosis is confirmed by Autism Diagnostic Interview (ADI-R)
- Subject demonstrates 'irritable' behaviors such as tantrums, aggression, self-injurious behavior, or a combination of such behaviors
- Subject's Aberrant Behavior Checklist (ABC) Irritability Subscale score is >=18
- Subject's Clinical Global Impressions – Severity (CGI-S) scale score is >=4 (4=moderately ill)
- Subject's current therapeutic/intervention plan for treating his or her autistic disorder (educational/behavioral or other therapy; medication use; dietary interventions) has

been consistent/stable over at least the past 3 months and the subject's caregiver agrees, and it is possible for, the subject to maintain his or her current therapeutic/intervention plan throughout participation in the clinical study.

- Subject's caregiver agrees, and it is possible for, the subject to abstain from partaking in <u>new</u> treatments to treat the subject's autistic disorder symptoms during participation in the study. This includes educational/behavioral therapy, dietary interventions, medications such as FDA-approved Risperdal® and Abilify® and other medications often prescribed for the treatment of other autism-related symptoms, such as anxiety, depression, or obsessive-compulsive disorder, including antipsychotic medications used to treat severe behavioral problem, and medications used to treat people with attention deficit disorder

EXCLUSION CRITERIA

- Subject has primary or concurrent diagnosis of another disorder or other identifiable genetic condition associated with the autism spectrum scale or with mental retardation, including:

  - ✓ PDD-NOS
  - ✓ Asperger's Disorder
  - ✓ Rett's Disorder
  - ✓ Fragile-X Syndrome
  - ✓ Childhood Disintegrative Disorder
  - ✓ Down Syndrome

- Seizure disorders (active), cerebrovascular disease or brain trauma as etiology of autistic behavior
- Current diagnosis of, and treatment for, bipolar disorder, psychosis, schizophrenia, or major depression
- Known neurological disease, such as encephalitis
- Significant sensory or motor impairment such as cerebral palsy
- Diagnosis of epilepsy that is currently treated with anti-convulsant medication
- Previous significant head trauma
- Hearing loss requiring use of assistive devices such as hearing aids or cochlear implant
- Significant visual impairment that cannot be adequately corrected with lenses
- Documented mental age younger than 18 months
- HIV and other autoimmune disorders
- Active cancer or treatment for cancer within last 6 months
- Unstable cardiac disease, such as a recent cardiac arrhythmia (including atrial fibrillation, ventricular fibrillation and irregular atrial-ventricular conduction time), or recent congestive heart failure, or recent myocardial infarction
- Previous surgical interventions to the head/neck area
- Sensitivity to, or contraindication for, light therapy
- Participation in a research study within the past 30 days

BASELINE ASSESSMENT

DEMOGRAPHICS AND TREATMENT HISTORY

(i) Demographic Variables

The following demographic variables will be recorded for each subject:

1. *Gender*: male or female.
2. *Age*
3. *Ethnicity*: Caucasian, Hispanic, African American, American Indian, Asian/Pacific Islander, Other.

(ii) Medication and Treatment History

A list of the following information about a subject's current and past medication and therapy use will be recorded:

- ✓ All prescription and OTC medications used to date to treat the subject's symptoms of autistic disorder. Include information on daily dosage and duration of use, as applicable:
  - Current medications
  - Non-current medications

- ✓ All therapies (conventional and alternative) used to date to treat the subject's symptoms of autistic disorder. Include information on frequency and duration of application, as applicable:
  - Current therapies
  - Non-current therapies

- ✓ All current medications (prescription and OTC) and therapies (conventional and alternative) currently used for non-autism disorder related indications. Include information on medication dosages and duration of use and frequency and duration of therapy applications, as applicable, as well as the indications for which each is being used.

BASELINE EVALUATION

The following tools from the Study Test Battery to be used during Study Baseline Assessment:

- ➢ Aberrant Behavior Checklist (ABC)
- ➢ Clinical Global Impressions (CGI) Severity of Illness Scale (CGI-S) only

PROCEDURE ADMINISTRATION PHASE

GENERAL ASSESSMENT CONDITIONS

- Subjects will be required to maintain their regular medication and dosage schedule used to treat symptoms related to autism disorder throughout the study. **Subjects will not be required to stop taking any medications used to treat their autism disorder symptoms or for any other indication, as already prescribed by a treating physician, throughout the duration of participation in the study.**
- Subjects must agree to not start taking any new medications, or partake in any other new non-study treatments, or to change the dosages they take of current medications, to treat the symptoms of autism disorder, during study participation.
- Subjects must agree to notify the study investigator immediately if their treating physician makes any change to medication, medication dosage or other treatment plan. The PI will evaluate the information to determine, in his or her professional opinion, if the changes are substantial enough to warrant withdrawal of the subject from further study participation.

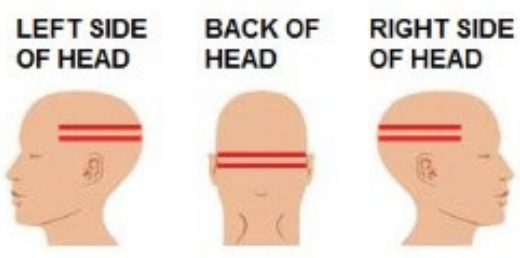
STUDY TREATMENT ADMINISTRATION PROTOCOL

- The study treatment administration phase will extend over four consecutive weeks.
- Each subject will receive a total of eight study treatments with the Erchonia® HLS laser device, two treatments per week for 4 consecutive weeks, each treatment administration 3 to 4 days apart.
- Each study treatment will be administered by the study investigator at the study test site.
- Each study treatment administration will last 5 continuous minutes.

The treatment administration process is as follows:

1. The patient is seated comfortably.
2. The patient is correctly fitted with the KenTek Corporation KGOG-6101 light blue Medium Goggles safety goggles.
3. The Erchonia® HLS laser is positioned perpendicular to and 4 inches above the skin surface of the right temporal region.
4. The laser is activated and applied systematically in a slow continuous free-hand sweeping motion laterally from the right temporal region across the back of the head to the left temporal region and back again across the same location on the back of the head to the right temporal region and so forth back and forth for 5 continuous minutes.

   The temporal region of the head is in the lateral regions of both the right and left sides of the head over the temporal bone, behind the eye between the forehead and the ear and above the zygomatic arch. The back of the head in this protocol is defined as the area across the base of the parietal bone of the cranium extending laterally between the bilateral temporal regions. The locations and treatment processes are illustrated in the image below.



5. HLS Spectrum laser is turned off.
6. The safety goggles are removed from the subject.
7. The treatment session is complete.

STUDY EVALUATION TIMELINE

The study evaluation phase is as follows:

- ✓ Treatment Administration Phase: 4 weeks
- ✓ Post-treatment Evaluation Phase:
  - 4 weeks for all subjects

The evaluation time points and associated measures to be evaluated during the study are as follows:

TREATMENT ADMINISTRATION PHASE: 4 WEEKS

At Each of the 8 Study Treatment Administration Visits

- ➢ Medication and therapy use review
- ➢ Adverse events evaluation

WEEK 2 END: Study Midpoint
Following completion of the first 2 weeks of the Treatment Administration Phase (after the 1st 4 treatments), the following study measures will be recorded:

- ➢ Aberrant Behavior Checklist (ABC)
- ➢ Clinical Global Impressions (CGI)

WEEK 4 END: Study Endpoint
Following completion of the 4-week Treatment Administration Phase (after completion of all 8 treatment administrations), the following study measures will be recorded:

- ➢ Aberrant Behavior Checklist (ABC)
- ➢ Clinical Global Impressions (CGI)
- ➢ Caregiver Satisfaction with Study Outcome
- ➢ Caregiver Perceived Group Allocation and Rationale
- ➢ Administration Investigator Perceived Group Allocation and Rationale

POST-TREATMENT EVALUATION PHASE

WEEK 8: All Subjects
Four weeks following completion of the 4-week Treatment Administration Phase (8 weeks after study onset), the following study measures will be recorded:

- Aberrant Behavior Checklist (ABC)
- Clinical Global Impressions (CGI)
- Medication and therapy use review
- Adverse events evaluation
- Caregiver Satisfaction with Study Outcome
- Caregiver Perceived Group Allocation and Rationale
- Administration Investigator Perceived Group Allocation and Rationale

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STATISTICAL ANALYSIS PLAN

The aim of this study is to determine if the treatment effect of the Erchonia® HLS laser device for the active treatment group is greater than that for the placebo treatment group.

The study will be considered a success if, using the Intent-To-Treat (ITT) Last Observation Carried Forward (LOCF) analysis, the primary endpoint is statistically significant at the 0.05 level.

PRIMARY EFFICACY OUTCOME MEASURE

The primary efficacy outcome measure in this study is the mean change from baseline to study endpoint (end of the four-week treatment period) in the Aberrant Behavior Checklist (ABC) Irritability Subscale score.

Study success will be established through the detection of a minimum mean difference of -8.5 points between test and placebo groups in the change in ABC Irritability Subscale score from baseline to study endpoint (end of treatment week 4) adjusted for the baseline ABC Irritability Subscale score. The -8.5-point mean difference between treatment groups is considered clinically relevant with a SD of 8.9, a two-sided test with 80% power and a 5% level of significance.

Null Hypothesis: There is no difference in the mean change in ABC Irritability Subscale score from baseline to study endpoint adjusted for the baseline ABC Irritability Subscale score between active treatment and placebo groups, to the effect of less than -8.5 points.

Alternative Hypothesis: There is a difference in the mean change in ABC Irritability Subscale score from baseline to study endpoint adjusted for the baseline ABC Irritability Subscale score between active treatment and placebo groups, to the effect of -8.5 points or greater.

Rationale for Primary Efficacy Outcome Measure

Determination, application and support of the detection of a mean difference of -8.5 points between test and placebo groups in the change in the ABC Irritability Subscale score from Baseline to study Endpoint adjusted for the baseline ABC Irritability Subscale score being considered clinically relevant is based on the results of the clinical study for Abilify® (aripiprazole) that resulted in FDA clearance of the drug for the same exact intended indication as in this proposed pivotal trial combined with the results of a feasibility study employing the Erchonia® HLS Laser Device with the same device output parameters and treatment administration protocol as proposed for the current pivotal study.

Abilify® (apriprazole) Study: In the Abilify® study, the primary efficacy endpoint was the mean change from Baseline to Week 8 LOCF in the ABC Irritability Subscale score. There was a statistically significant difference between the treatment groups in favor of Abilify® (aripiprazole) in the adjusted mean change from Baseline to Week 8 LOCF (study Endpoint) in the ABC Irritability Subscale score of -7.9 (placebo -5.0, aripiprazole -12.9, difference -7.9, 95% CI (-11.7, -4.1), $p<0.001$). It was concluded that this change demonstrated clinically relevant and statistically significant improvement compared with placebo on the primary efficacy endpoint in the adjusted mean change from Baseline on the ABC Irritability Subscale at Endpoint.

FDA independent analysis concluded that the results of the clinical trials showed that treatment with aripiprazole is efficacious in improving the symptoms of irritability in children and adolescents with autism, as demonstrated by the results on the primary endpoint, ABC Irritability Subscale. It was stated that **aripiprazole showed clinically meaningful and statistically significant improvement compared with placebo** through study Endpoint evaluation on the primary efficacy measure of mean change from Baseline to Week 8 in the ABC Irritability Subscale score.

Therefore, the clinically significant effect size of the Erchonia® HLS Laser Device as applied to children and adolescents with autistic disorder in the proposed clinical study based on prior experience and research is defined as a minimum mean difference of -8.5 points on the ABC Irritability Subscale score from baseline to endpoint (week four) between active and placebo treatment groups.

SECONDARY EFFICACY OUTCOME MEASURES
The following secondary efficacy outcome measures will be evaluated in this study:

- *Positive Response Rate*: Difference in Positive Response Rate between treatment groups, where 'Positive Response Rate' is defined as satisfaction of both of the following 2 criteria:
  - ✓ >= 25% reduction from baseline to endpoint in the Aberrant Behavior Checklist (ABC) Irritability Subscale score based on the subject's primary caregiver's rating; AND
  - ✓ Clinical Global Impressions – Improvement (CGI-I) scale rating of 1 or 2 (much improved or very much improved) at study endpoint as determined by the clinician's evaluation

- Mean change from baseline to endpoint in the other 4 ABC Subscale scores, based on ratings by the subject's primary caregiver:
  - ✓ Lethargy/Social Withdrawal
  - ✓ Stereotypic Behavior
  - ✓ Hyperactivity/Noncompliance
  - ✓ Inappropriate Speech

- Mean change from baseline to endpoint in the global ABC score
- Change in ratings on the CGI-S from baseline to study endpoint evaluation
- Change in ratings on the CGI-I from baseline to study endpoint evaluation
- Caregiver Satisfaction with Study Outcome ratings between treatment groups and across evaluations

STATISTICAL METHODS

Efficacy analysis will be according to the intent to treat (ITT) principle by last observation carried forward (LOCF).

Intent to Treat: Subjects will be included in the ITT analysis if they complete their baseline clinical assessments and had at least one post-randomization efficacy evaluation and corresponding baseline value.

Last observation carried forward (LOCF): Missing data will be handled by carrying forward the last observation for the relevant measure. The LOCF data set included date recorded at a given time point, or, if no observation was recorded at that time point, data carried forward from the previous time point with available data. Baseline data will not be carried forward or averaged to impute missing values for the LOCF data set.

STATISTICAL ANALYSIS

Primary Efficacy Analysis

For the continuous primary efficacy measure of ABC Irritability Subscale score, change scores will be evaluated by analysis of covariance (ANCOVA). The ANCOVA models for LOCF data sets will include the baseline measure as a covariate and treatment (active of placebo) as main effects.

Secondary Measures Analysis

- For the continuous secondary efficacy measures of the other 4 ABC Subscale scores, and the Global Score, change scores will be evaluated by analysis of covariance (ANCOVA). The ANCOVA models for LOCF data sets will include the baseline measure as a covariate and treatment (active of placebo) as main effects. A two-way significance level of 5% will be considered statistically significant.

- The categorical measures of the CGI will be analyzed within the framework of the generalized Cochran-Mantel Haenszel (CMH) procedure.

- Responder rate will be evaluated using Fisher's exact test to compare the proportion of responder rates between the test and control groups.

P-values will be 2-tailed tests of significance rounded to 3 decimal places. All analyses will be performed at the 5% significance level.

CAREGIVER SATISFACTION

Caregiver satisfaction ratings will be descriptively presented through the number and percentage of responses per response category. Fischer's Exact Test will be employed to determine the significance of the difference in categorical responses between treatment groups.

BLINDING EFFICACY EVALUATION

Blinding efficacy evaluation will be conducted through analysis of findings from the Caregiver and the Assessment Investigator Perceived Subject Group Allocation and Rationale responses, recorded at completion of the procedure administration phase (study endpoint).

Statistical evaluation of blinding efficacy will be performed as follows:

(i) The percentage of caregivers who correctly perceived the subject's procedure group assignment and the percentage of caregivers who did not correctly perceive the subject's procedure group assignment will be calculated.

(ii) The percentage of times the assessment investigators correctly perceived subjects' procedure group assignment and the percentage of times the assessment investigators did not correctly perceive subjects' procedure group assignment will be calculated.

(iii) The **Fischer's Exact categorical analysis technique** for comparison of proportion of successes (accurate procedure group assignment determination) and failures (inaccurate procedure group assignment determination) between subject

groups will be performed for each of the caregiver and assessment investigator determinations.

(iv) **Qualitative analysis confirmation:** Evaluation of the comments provided by the caregiver and assessment investigators in the rationale section to explain the guess at group assignment will be evaluated and interpreted as follows to either support or negate the numerical findings:

- *Positive blinding efficacy* will be supported through qualitative assessment of comments provided to support perceived group assignment that pertain to the determination being made based on treatment efficacy or lack thereof; e.g.: 'My child has been calmer and communicating better lately, so I think he got the real treatment' or 'I haven't noticed any change in my child's behavior at all, so I believe he got the fake treatment.'
- *Blinding will be determined to have failed* if comments provided to support perceived group assignment pertain to factors such as sensation/visual clues, such as 'I saw/didn't see a light go on the laser', or other factors that pertain to blinding having been compromised such as 'I overheard the doctor saying my child was/wasn't getting the real treatment.'

SAFETY ANALYSES

Safety analyses will be completed on all subjects who were randomized to treatment group and received at least the first study treatment administration with the Erchonia® HLS Laser device.

Safety will be assessed by evaluating and comparing frequency and incidence of observed and/or reported adverse events between test and placebo treatment groups. A chi-square test with a continuity correction will be performed to compare the percentage of subjects who had adverse events and/or reactions between the test and placebo group subjects.

SAFETY AND CONFIDENTIALITY ISSUES

ADVERSE EVENTS

At any time throughout the study, any adverse event reported by a subject and/or subject's caregiver and/or observed by the study investigator will be recorded on the case report form and subsequently evaluated by the Principal Investigator for its relation to the study treatment and whether or not any corrective action need be taken. All applicable adverse events will be reported to the IRB and EC, if applicable.

Formal evaluation of the occurrence of any adverse events will take place at the end of each study treatment administration and each evaluation visit. In addition, subjects/caregivers will be instructed to contact the investigator at any other time that he or she believes a potential adverse event has occurred throughout the subject's participation in the clinical study.

The investigator will record the observation or report of any adverse event and assign the relationship to the study treatment on the appropriate case report form in the subject's file and will report the occurrence to the governing IRB, if and as appropriate,

within 5 days of the reported occurrence, or within 24 hours in the occurrence of a serious adverse event including death.

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® HLS at the test site, both the subject and the administration investigator will wear safety glasses that filter out the laser light spectrum. The administration investigator will wear KenTek Corporation KenTek C22-KMT-6101 light blue safety glasses and the subject will wear KenTek Corporation KGOG-6101 light blue Medium Goggles safety goggles. Additional information on this safety eyewear is contained above on pages 6-8 under the section titled: DEVICE SAFETY: RISK AND PREVENTION OF EYE INJURY.

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. However, potential adverse events that may occur include, but are not necessarily limited to: skin irritation, skin discoloring, skin rash, skin indentations and infection. There may also be unknown or unanticipated risks to using the laser devices with this study treatment.

MONITORING OF THE CLINICAL STUDY

Prior to commencement of the study at any test site, 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® HLS to the study population for all study staff involved parties. A formalized Clinical Trial Monitoring Plan will be in place for real time, remote and on-site monitoring, as applicable, that will be strictly followed to ensure on-going compliance and accuracy of procedures at the test site(s).

SUBJECT PRIVACY AND CONFIDENTIALITY

Records for each subject in the study will be maintained in separate files in a locked filing cabinet at the test site. The Principal Investigator will be responsible for ensuring that all records for a subject are stored in that subject's file at all times other than when information is being recorded on them.

Once a subject's participation in the study is complete and all of the required records are in the subject's file, copies of the documents may be made and supplied to the study Sponsor who will store them in a locked filing cabinet. Copies of subjects' case report forms will also be sent to Regulatory Insight, Inc. for the purpose of monitoring the data collection process and analysis of results. Regulatory Insight, Inc. will also maintain these copies in a separate clinical study file that is kept in a locked filing cabinet. The original records will be maintained at the 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 subject ID upon acceptance into the study. The subject ID will comprise the investigator's first and last name initials and a three-digit number that will be determined based upon the subject's order of entry into the study. For example, the eighth subject to be enrolled under Principal Investigator Marvin Boris will have a subject ID of MB008. Neither the study

Sponsor nor Regulatory Insight, Inc. will receive any 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.

INFORMED CONSENT

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

The informed consent form can be found in **Appendix B.**

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.**

MODEL: ERCHONIA® HLS

TRADE NAME: SPECTRUM BY ERCHONIA™

A double-blind, placebo-controlled randomized evaluation of the effect of the Erchonia® HLS laser device on children with autistic disorder clinical study protocol 2

ERCHONIA CORPORATION

Version 1.3
September 16, 2020

INFORMED CONSENT FORM

RESEARCH SUBJECT'S CAREGIVER INFORMATION AND CONSENT FORM

TITLE:	A Double-Blind, Placebo-Controlled Randomized Evaluation of the Effect of the Erchonia® HLS Laser Device on Children 2 with Autistic Disorder
PROTOCOL NO.:	Version 1.3; September 16, 2020
SPONSOR:	Erchonia Corporation Melbourne, Florida United States
INVESTIGATOR:	<PI name> <PI address>
SITE(S):	<Site name>
STUDY-RELATED PHONE NUMBER(S):	<PI name> <PI phone> (24 hours)

This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

SUMMARY

You are being asked to have your child take part in a research study because your child has autism. The purpose of this consent form is to help you decide if you want your child to be in the research study and if you are able to take part as your child's caregiver in this study. Please read this form carefully. For your child to be in a research study you must give your informed consent. "Informed consent" includes:

- Reading this consent form,
- Having the study doctor or staff explain the research study to you,
- Asking questions about anything that is not clear, and
- Taking home an unsigned copy of this consent form. This gives you time to think about it and to talk to family or friends before you make your decision.

You should not join this research study until each of your questions are answered.

Things to know before deciding to take part in a research study:

- The main goal of a research study is to learn things to help patients in the future.
- The main goal of regular medical care is to help each patient.
- No one can promise that a research study will help you or your child.
- Taking part in a research study is entirely voluntary. No one can make you take part.
- If you decide to take part, you can change your mind later on and withdraw from the research study.
- The decision to join or not join the research study will not cause you or your child to lose any medical benefits. If you decide not to take part in this study, your doctor will continue to treat your child.
- This study involves experimental (investigational) device procedures that are being tested for a certain condition or illness. An investigational device is one that has not been approved by the U.S. Food & Drug Administration (FDA).

After reading and discussing the information in this consent form you should know:

- Why this research study is being done;
- What will happen during the research;
- What device and procedures will be used;
- Any possible benefits to you or your child;
- The possible risks to you or your child;
- The other medical procedures, drugs or devices that could be used instead of being in this research study; and
- How problems will be treated during the study and after the study is over.

If you take part in this research study, you will be given a copy of this signed and dated consent form.

PURPOSE OF THE STUDY

In this study, the Sponsor, Erchonia Corporation, and investigators are studying the use of a device called the Erchonia® HLS that gives off low level laser light. This study is to see if using the Erchonia® HLS can help to improve symptoms associated with autistic disorder in children aged five through twelve years.

PROCEDURES

- If you agree to let your child take part in this study, he or she will be one of about 40 children taking part.
- This is a randomized, double-blind, placebo-controlled study. This means that if you choose to let your child take part in this study, it will be determined by chance (like the flip of a coin) whether your child will get the active study treatment or the placebo study treatment. In this study, there will be two groups of participants. Participants in one of the groups will get active study treatments. The other group of participants will get a placebo treatment. This means that the study treatments will be 'fake' as if the Erchonia® HLS laser device were turned off.

  Since there are two different groups, your child has:
  - About a 50% chance of receiving active study treatments
  - About a 50% chance of receiving a placebo treatment (no laser therapy).

  Neither the active nor the placebo device make any noise or produce any heat, and both will have a light that can be seen, so neither you, your child nor the study investigators will be able to guess which group your child is in.

For your child to take part in this study, you must agree to have him or her keep taking the medications he or she are taking right now and to keep doing other treatments and therapies he or she is doing right now to help with the symptoms of autistic disorder. You must also agree to not permit your child to take any new medicines or try any other new treatments or therapies to help with the symptoms of autistic disorder until his or her part in the study is over. If your doctor makes a change to your child's medication, you must agree to tell the study doctor right away.

- The study takes about eight weeks to complete.
- The study process is as follows:

Screening Visit (Visit 1)

If you are interested in taking part in this research study, we will conduct a screening visit at the test site. At this visit, we will review this informed consent document. Then we will:

- Get information about your child's autistic disorder, and about medications and treatments he or she is doing now and has done in the past to treat the symptoms of autistic disorder
- Get information about your child's other medical history, including information about other current medical conditions he or she may have
- Get information about other medicines your child is taking or has taken in the past

- Do an interview with questions about your child's family, medical, developmental and education background; communication and social skills; and behavior patterns and interests
- Rate how severe your child's autistic disorder is on a scale from 1 (normal) through 7 (amongst the most severe instances)
- Have you complete a questionnaire about the signs and symptoms of your child's autistic disorder

- Get information about your child's age, gender, and ethnicity

  This visit will take about 2 hours.

Treatment Phase (Visits 2 through 9)
The treatment phase will start once you have successfully completed the screening procedures, and we can confirm that your child is eligible for this study.

You will need to bring your child to the test site eight times over four weeks for eight treatments with the Erchonia® HLS Laser device. This is two times each week. Each treatment session takes about five minutes. Your child will sit in a chair. The laser light will shine across your child's head back and forth from right to left, but the laser will not touch your child's skin. Your child will wear special goggles that block out the light from the laser device.

At each treatment visit, we will ask you if there have been any changes in the medicines your child is taking or in the treatments your child is doing. This should take a few minutes.

After the fourth treatment with the Erchonia® HLS, we will again:

- Have you complete a questionnaire about the signs and symptoms of your child's autistic disorder
- Rate how severe your child's autistic disorder is on a scale from 1 (normal) through 7 (amongst the most severe instances), and rate any improvement in the symptoms of your child's autistic disorder since starting the study on a scale from 1 (very much improved) through 7 (very much worse).

  This should take about 15-20 minutes.

After the eighth and last treatment with the Erchonia® HLS, we will again:

- Have you complete a questionnaire about the signs and symptoms of your child's autistic disorder
- Rate how severe your child's autistic disorder is on a scale from 1 (normal) through 7 (amongst the most severe instances), and rate any improvement in the

symptoms of your child's autistic disorder since starting the study on a scale from 1 (very much improved) through 7 (very much worse)

This should take about 15-20 minutes.

Post-treatment Phase (Visit 10)
Four weeks after your last treatment with the Erchonia® HLS laser, you will need to bring your child to the test site (visit 10), where we will again:

- Have you complete a questionnaire about the signs and symptoms of your child's autistic disorder
- Rate how severe your child's autistic disorder is on a scale from 1 (normal) through 7 (amongst the most severe instances), and rate any improvement in the symptoms of your autistic disorder since starting the study on a scale from 1 (very much improved) through 7 (very much worse)
- Ask you if there have been any changes in the medicines your child is taking or in the treatments your child is doing

This should take about 20 minutes.

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RISKS AND DISCOMFORTS
The complete risk profile or anticipated risks with the use of the Erchonia® HLS laser device is not known. However, there may be risks to using the device with this study procedure such as skin irritation, itching, discoloring, rash, indentations, pain/discomfort and infection.

It is possible that your child will not get any improvement in the symptoms of autistic disorder or that he or she may even get worse.

NEW INFORMATION
You will be told about any new information that might change your decision to have your child be in this study. You may be asked to sign a new consent form if this occurs.

BENEFITS
The symptoms of your child's autistic disorder may lessen while in this study; however, this cannot be promised. The results of this study may help to improve symptoms of autistic disorder for other people in the future.

COSTS
It will not cost you or your child anything to be part of the study. Erchonia Corporation, the sponsor of this research will provide use of the Erchonia® HLS laser device to do the study treatment free of charge during this study. The cost for all study-related

procedures and measurements will also be covered by Erchonia Corporation. Nothing will be billed to you or to your insurance company.

PAYMENT FOR PARTICIPATION
You will not be paid for your or your child's part in this research study.

ALTERNATIVE TREATMENT
If you decide not to have your child enter this study, there is other care available to your child, such as educational, behavioral and dietary intervention programs and treatment plans, and medications such as Risperdal® and Abilify®. The study doctor will discuss these with you. You do not have to be in this study to have your child be treated for the symptoms of his or her autistic disorder.

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

What information may be used and given to others?
The study doctor will get your child's personal and medical information. For example:

- Research records
- Records about your child's study visits.

Who may use and give out information about your child?
The study doctor and the study staff

Who might get this information?
The sponsor of this research. "Sponsor" means any persons or companies that are:

- working for or with the sponsor, or
- owned by the sponsor

Your child's information <u>may</u> be given to:

- The U.S. Food and Drug Administration (FDA),
- Department of Health and Human Services (DHHS) agencies,
- Governmental agencies in other countries,
- Institutional Review Board (IRB)
- 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 information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Why will this information be used and/or given to others?

- to do the research,
- to study the results, and
- to see if the research was done right

If the results of this study are made public, information that identifies your child will not be used.

What if I decide not to give permission to use and give out my child's health information?
Then your child will not be able to be in this research study.

May I review or copy my child's information?
Yes, but only after the research is over.

May I withdraw or revoke (cancel) my permission?
Yes, but this permission will not stop automatically.

You may withdraw your child from the study or take away your permission to use and disclose your child's health information at any time. You do this by sending written notice to the study doctor. If you withdraw your permission, your child will not be able to stay in this study.

When you withdraw your permission, no new health information identifying your child will be gathered after that date. Information that has already been gathered may still be used and given to others.

Is my child's health information protected after it has been given to others?
There is a risk that your child's information will be given to others without your permission.

COMPENSATION FOR INJURY
If your child is injured or gets sick as a result of being in this study, call the study doctor immediately. The study doctor will provide emergency medical treatment. Your insurance will be billed for this treatment. The sponsor will pay any charges that your insurance does not cover. No other payment is routinely available from the study doctor or sponsor.

VOLUNTARY PARTICIPATION AND WITHDRAWAL
You and your child's participation in this study is voluntary. You may decide not to have your child participate, or you may withdraw your child from the study at any time. Your decision will not result in any penalty or loss of benefits to which you or your child are otherwise entitled.

Your child's participation in this study may be stopped at any time by the study doctor or the sponsor without your consent for any of the following reasons:

- if it is in your child's best interest;

- you do not consent to your child continuing in the study after being told of changes in the research that may affect your child;
- or for any other reason

If your child leaves the study before the planned final visit, you may be asked by the study doctor to have your child complete some of the end of study procedures.

SOURCE OF FUNDING FOR THE STUDY
The sponsor, Erchonia Corporation, will pay for this research study.

QUESTIONS
Contact <PI name> at <PI phone #> for any of the following reasons:

- if you have any questions about this study or you or your child's part in it,
- if you feel your child has had a research-related injury or a bad reaction to the study treatment, or
- if you or your child have questions, concerns or complaints about the research

If you have questions or concerns about your child's rights as a research subject or if you have questions, concerns or complaints about the research, you may contact:

<IRB name>
<IRB address>
<IRB Telephone>
<IRB e-mail>

<IRB name> is a group of people who independently review research.
<IRB name> will not be able to answer some study-specific questions, such as questions about appointment times. However, you may contact <IRB name> if the research staff cannot be reached or if you wish to talk to someone other than the research staff.

Do not sign this consent form unless you have had a chance to ask questions and have gotten satisfactory answers.

If you agree to have your child be in this study, you will receive a signed and dated copy of this consent form for your records.

CONSENT
I have read this consent form (or it has been read to me). All my questions about the study and my and my child's part in it have been answered. I freely consent to have my child be in this research study.

I authorize the use and disclosure of my child's health information to the parties listed in the authorization section of this consent for the purposes described above

By signing this consent form, I have not given up any of my or my child's legal rights.

_____
Subject Name (printed)

CONSENT SIGNATURE:

_____ _____
Signature of Legally Authorized Representative, Parent or Guardian Date

_____
Authority of Subject's Legally Authorized Representative or Relationship to Subject

_____ _____
Signature of Person Conducting Informed Consent Discussion Date

ASSENT SECTION For Subjects Ages [5] - [12]:

Statement of person conducting assent discussion:

1. I have explained all aspects of the research to the subject to the best of his or her ability to understand.
2. I have answered all the questions of the subject relating to this research.
3. The subject agrees to be in the research.
4. I believe the subject's decision to enroll is voluntary.
5. The study doctor and study staff agree to respect the subject's physical or emotional dissent at any time during this research when that dissent pertains to anything being done solely for the purpose of this research.

_____ _____

Signature of Person Conducting Assent Discussion | Date

Statement of Parent or Guardian:

My child appears to understand the research to the best of his or her ability and has agreed to participate.

_____ _____

Signature of Parent or Guardian | Date

RESEARCH SUBJECT INFORMATION SHEET FOR CHILDREN:

TITLE:	A Double-Blind, Placebo-Controlled Randomized Evaluation of the Effect of the Erchonia® HLS Laser Device on Children with Autistic Disorder 2
PROTOCOL NO.:	Version 1.3; September 16, 2020
SPONSOR:	Erchonia Corporation Melbourne, Florida United States
INVESTIGATOR:	<PI name> <PI address>
SITE(S):	<Site name>
STUDY-RELATED PHONE NUMBER(S):	<PI name> <PI phone> (24 hours)

You are being asked to take part in a research study because you have autistic disorder.

Our study device is called the Erchonia® HLS Laser device. We do not know if it is better than other treatments for autistic disorder, so we are asking you to help us with this research study. The treatment with the Erchonia® HLS Laser device might not make you feel better, or it may even make you feel worse.

This study will last eight weeks. You will have to come to the study center ten times. You will be asked questions about your autistic disorder, about your behaviors, about things you like to do and how you get along with other people.

You will need to come to the study center two times each week for four weeks in a row to get a treatment with the Erchonia® HLS Laser device.

If the treatment makes you feel different, or if you get itching, rash, tingling or other skin marks or feelings where the laser light shined on your skin, you must tell your parents or the study doctor.

Important things to know:

- You don't have to do this if you don't want to.
- We won't be mad at you if you decide you don't want to do this.
- Your doctor will still take care of you even if you don't want to do this.

If later you have any questions about this study, please ask your parents or call the study doctor (<name of doctor>) or his nurse at <test site phone #>.

CONSENT SIGNATURE:

_____ _____
Signature of Legally Authorized Representative, Parent or Guardian — Date

_____
Authority of Subject's Legally Authorized Representative or Relationship to Subject

_____ _____
Signature of Person Conducting Informed Consent Discussion — Date

ASSENT SECTION For Subjects Ages [5] - [12]:
Statement of person conducting assent discussion:

1. I have explained all aspects of the research to the subject to the best of his or her ability to understand.
2. I have answered all the questions of the subject relating to this research.
3. The subject agrees to be in the research.
4. I believe the subject's decision to enroll is voluntary.
5. The study doctor and study staff agree to respect the subject's physical or emotional dissent at any time during this research when that dissent pertains to anything being done solely for the purpose of this research.

_____ _____
Signature of Person Conducting Assent Discussion — Date

Statement of Parent or Guardian:

My child appears to understand the research to the best of his or her ability and has agreed to participate.

_____ _____
Signature of Parent or Guardian — Date