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 and adolescents with autistic disorder clinical study protocol

ERCHONIA CORPORATION

Version 2.0
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STUDY INFORMATION

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ETHICS COMMITTEE

Research Ethics Committee of the Havana Institute of Neurology and Neurosurgery.

PURPOSE OF STUDY

The purpose of this clinical (pivotal) study is to demonstrate the efficacy of the Erchonia® HLS laser device, manufactured by Erchonia Corporation (the Sponsor), for the treatment of irritability associated with autistic disorder in children and adolescents aged five (5) to seventeen (17) 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 and adolescents aged five to seventeen years, inclusive.”

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 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 Health (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.

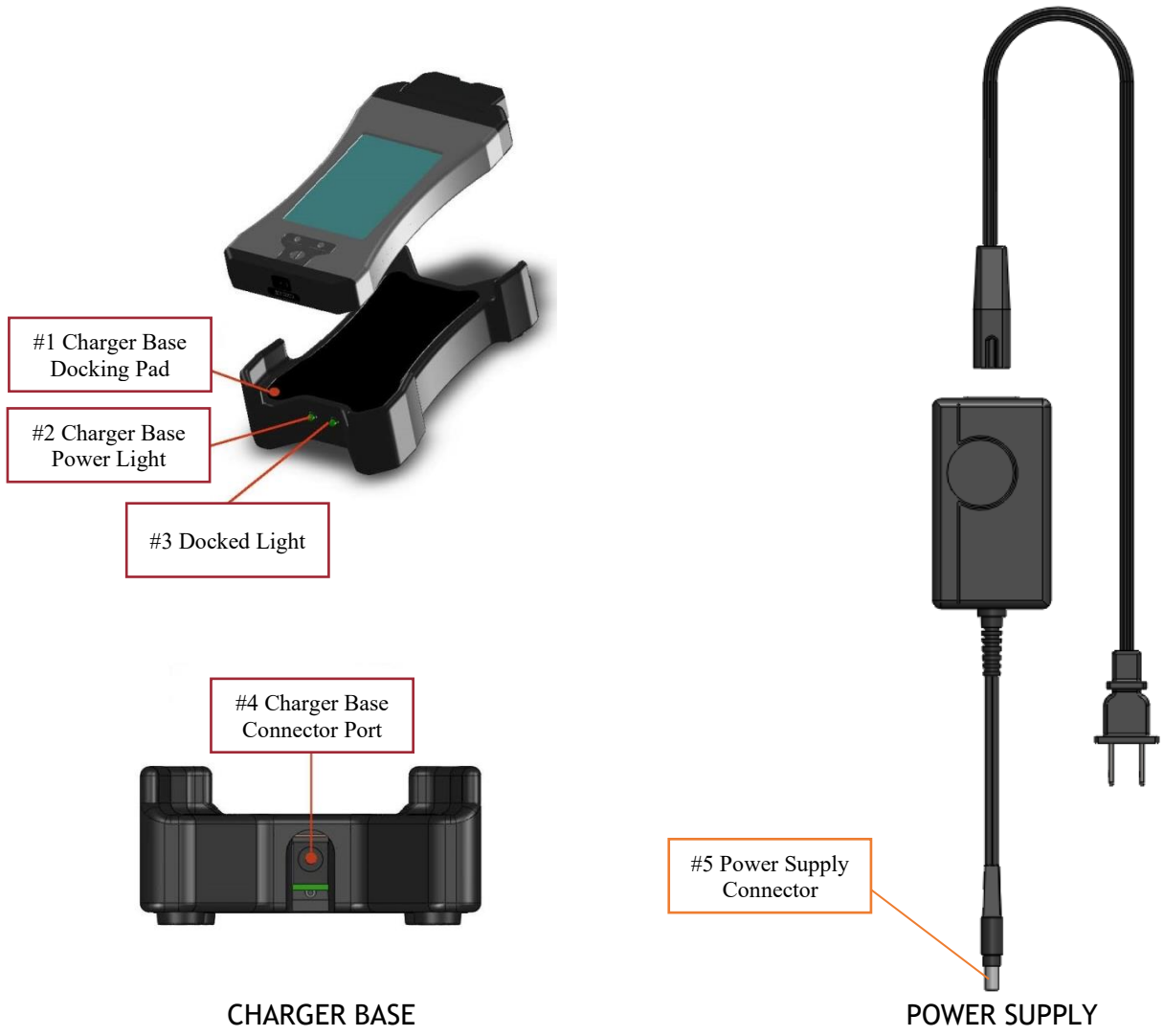


Figure 2: The Erchonia HLS Laser Charger Base and Power Supply

#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.

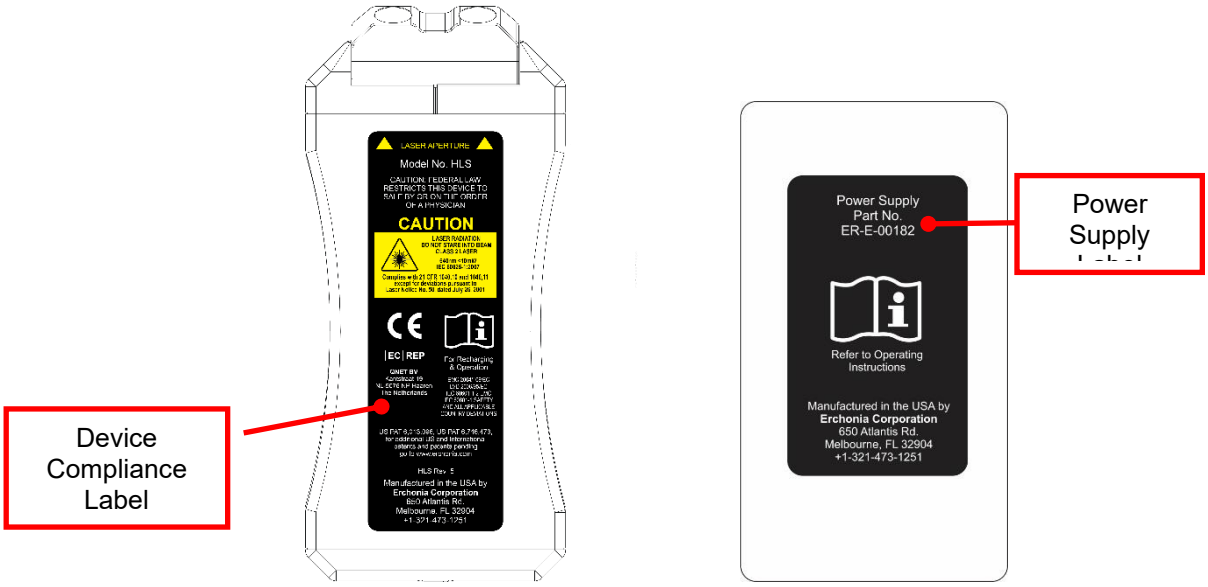
#4 CHARGER BASE CONNECTOR PORT
The Charger Base Connector Port is the location where the Power Supply Connector is plugged into for charging.

#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.



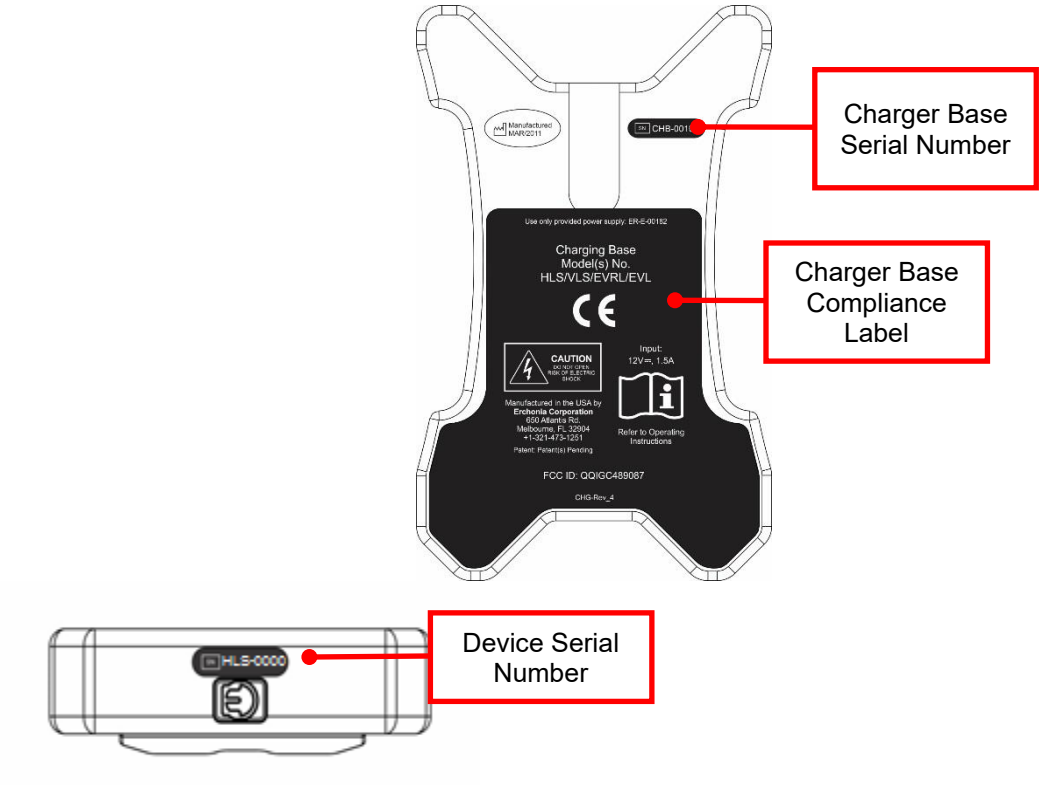


Figure 3: Erchonia HLS Laser **L**abeling

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 all of these pivotal trials, the active device, regardless of the device name employed, 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 all 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. A number of 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 hHLSthcare 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*: A number of 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 particular 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 revHLSed 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. As a consequence, 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 hHLSth 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 revHLSed 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 is able to 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.

Presently, the exact mechanism of LLLT remains enigmatic, and it remains unclear the impact this technology can have on genetic aberrations. Nevertheless, 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 neovascularization to name a few. Accordingly, auspicious positioning of laser along impaired regions of an autistic brain could elicit a positive therapeutic outcome.

SUPPORTIVE CLINICAL DATA: ERCHONIA® HLS FEASIBILITY PROOF OF CONCEPT TRIAL

BACKGROUND

In September 2012, a **feasibility proof of concept trial** based on the design - including device specifications and output, and treatment administration protocol parameters - was completed that evaluated the exact same indication proposed in this pivotal clinical trial. The feasibility proof of concept trial successfully established safety and potential effectiveness of the Erchonia® HLS Laser Device for the proposed indication for use of: “The Erchonia® HLS laser device is indicated to improve the symptoms of irritability associated with autistic disorder in children and adolescents aged five to seventeen years, inclusive.”

STUDY DESIGN

The feasibility proof of concept trial was conducted as a pilot study that employed the same parameters of the currently proposed full-scale pivotal trial protocol including the Erchonia® HLS Laser Device and its output parameters, the device application with respect to the

treatment administration protocol (number, frequency and duration of treatment administrations, etc.); and the study qualification enrollment criteria.

As the study was conducted as a feasibility study, all subjects received the active device treatments with the Erchonia® HLS Laser Device.

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).

SUBJECT SAMPLE

In the feasibility study, 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 all of the study qualification criteria were enrolled.

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 with respect to the proposed primary efficacy outcome measure of change on the ABC Irritability Subscale score for the proposed full-scale pivotal trial.

(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 for each of the 5 ABC Subscale Scores and the Global Score.

Table 1: Mean & standard deviation of Baseline and Endpoint ABC Subscale and Global Scores

	Baseline (n=11)		**Endpoint (n=11)**	
	Mean	**St. Dev.**	**Mean**	**St. Dev.**
Subscale I: Irritability/Agitation	14.45	8.18	5.36	6.70
Subscale II: Lethargy/Social Withdrawal	11.36	7.16	4.00	4.31
Subscale III: Stereotypic Behavior	7.36	5.20	3.64	3.23
Subscale IV: Hyperactivity & Noncompliance	18.00	11.93	6.91	6.20
Subscale V: Inappropriate Speech	6.18	3.37	2.73	1.35
Global Score	***57.36***	***31.56***	***22.64***	***19.22***

(ii) Change in ABC Subscale and Global Scores

Table 2 below shows the mean, standard deviation and per cent (%) of the change in scores from Baseline to Endpoint evaluation for each of the 5 ABC Subscale Scores and the Global Score.

Table 2: Mean, standard deviation & per cent (%) of Baseline to Endpoint change in ABC Subscale and Global Scores

	Mean Change	Std. Dev. of Change	Per cent (%) Change
Subscale I: Irritability/Agitation	-9.09	6.76	-62.89%
Subscale II: Lethargy/Social Withdrawal	-7.36	5.64	-64.80%
Subscale III: Stereotypic Behavior	-3.73	3.55	-50.62%
Subscale IV: Hyperactivity & Noncompliance	-11.09	9.40	-61.62%
Subscale V: Inappropriate Speech	-3.45	2.46	-55.88%
Global Score	***-34.73***	***25.84***	***-60.54%***

(iii) Statistical Analysis of the Change in ABC Subscale and Global Scores

a) T-tests for two correlated samples: 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.

The t-test results are shown in Table 3 below.

Table 3: 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***

b) ANOVA analysis: A series of ANOVAs for 2 correlated samples was conducted to confirm the statistical significance of the changes in Baseline to Endpoint ABC Subscale and Global scores identified through the t-test analyses. The Baseline to Endpoint statistically significant changes were confirmed for all 5 Subscale scores and the Global Score of the ABC. The ANOVA results are shown in Table 4 below.

Table 4: ANOVA results for Baseline to Endpoint changes in ABC Subscale and Global Scores

	$\mathcal{F}$	p(two-tailed)	p
Subscale I: Irritability/Agitation	19.90	0.0012	p<0.005
Subscale II: Lethargy/Social Withdrawal	18.72	0.0015	p<0.005
Subscale III: Stereotypic Behavior	12.11	0.0059	p<0.01
Subscale IV: Hyperactivity & Noncompliance	15.33	0.0029	p<0.005
Subscale V: Inappropriate Speech	21.62	0.00091	p<0.001

Global Score	***19.87***	***0.0012***	***p<0.005***

(iv) Individual Subject Results for ABC Subscale and Global Scores

Tables 5 through 10 below shows the Baseline, Endpoint and change scores for each individual study subject for each of the 5 Subscale scores and for the Global Score on the ABC

Table 5: Baseline, Endpoint and change scores for **ABC Subscale I: Irritability/ Agitation** by individual study subject

Subject	Baseline	Endpoint	Change
1	10	2	-8
2	14	6	-8
3	9	1	-8
4	8	0	-8
5	5	0	-5
6	5	5	0
7	23	23	0
8	25	11	-14
9	11	2	-9
10	24	6	-18
11	25	3	-22

Table 6: Baseline, Endpoint and change scores for **ABC Subscale II: Lethargy/ Social Withdrawal** by individual study subject

Subject	Baseline	Endpoint	Change
1	11	2	-9
2	3	1	-2
3	2	0	-2
4	6	0	-6
5	14	3	-11
6	7	7	0
7	12	12	0
8	17	5	-12
9	10	0	-10
10	16	3	-13
11	27	11	-16

Table 7: Baseline, Endpoint and change scores for **ABC Subscale III: Stereotypic Behavior** by individual study subject

Subject	Baseline	Endpoint	Change
1	8	3	-5
2	5	3	-2
3	3	1	-2
4	0	0	0
5	8	2	-6
6	3	3	0
7	11	11	0
8	17	8	-9
9	3	1	-2
10	9	4	-5
11	14	4	-10

Table 8: Baseline, Endpoint and change scores for **ABC Subscale IV: Hyperactivity & Noncompliance** by individual study subject

Subject	Baseline	Endpoint	Change
1	18	5	-13
2	8	4	-4
3	4	0	-4
4	4	0	-4
5	19	3	-16
6	4	4	0
7	21	21	0
8	37	13	-24
9	28	11	-17
10	21	8	-13
11	34	7	-27

Table 9: Baseline, Endpoint and change scores for **ABC Subscale V: Inappropriate Speech** by individual study subject

Subject	Baseline	Endpoint	Change
1	5	2	-3
2	7	3	-4
3	7	3	-4
4	0	0	0
5	7	2	-5
6	4	4	0
7	2	2	0
8	11	5	-6
9	6	2	-4

10	11	4	-7
11	8	3	-5

Table 10: Baseline, Endpoint and change scores for the **ABC Global Score** by individual study subject

Subject	Baseline	Endpoint	Change
1	52	14	-38
2	37	17	-20
3	25	5	-20
4	18	0	-18
5	53	10	-43
6	23	23	0
7	69	69	0
8	107	42	-65
9	58	16	-42
10	81	25	-56
11	108	28	-80

CONCLUSION

In summary, for the 11 subjects in this feasibility study, a pilot version based on this proposed full-scale pivotal clinical study protocol, 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. Decreased scores on the ABC indicate improvement in symptoms of the disorder under evaluation, in this case, Autistic Disorder.

Therefore, the results of this feasibility study indicate that low level laser therapy may be effective in improving the symptoms of autistic disorder in children and adolescents.

Additionally, 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, but rather 9 of the 11 subjects evidenced improvement on all Subscale scores and the Global Score while the remaining 2 subjects evidenced no change, establishing safety of the Erchonia® HLS Laser Device for the proposed indication.

SUPPORTIVE SCIENTIFIC DATA

Many physicians and other qualified behavioral intervention medical professionals report the application of low level laser light therapy to treating numerous neurological conditions including autistic disorder, and anecdotal reports from both physicians and patients are numerous and positive.

The following abstract pertains to a pilot study conducted to evaluate the application of laser-acupuncture to improving the symptoms of autistic disorder and provides scientific support for the efficacy of such treatment intervention for this indication

- **Laser-acupuncture for autism/autism spectrum disorder: a randomized sham controlled trial**
  Shahzad Anwar, Anwar Shah's First C.P. and Paralysis Clinic and Research Ctr. (Pakistan)

  Children with ASD were randomly separated into two groups: one receiving laser-acupuncture (LA) group (n=60) and the other sham laser-acupuncture (SLA) group (n=56), matched by age and severity of autism. The LA group received laser-acupuncture for selected acupoints while the SLA group received sham laser-acupuncture. A total of 24 LA and SLA sessions over 12 weeks were given. Primary outcome measures included Functional Independence Measure for Children (WeeFIM), Pediatric Evaluation of Disability Inventory (PEDI), Leiter International Performance Scale- Revised (Leiter-R), and Clinical Global Impression- Improvement (CGI-I) scale. Secondary outcome measures consisted of Aberrant Behavior Checklist (ABC), Ritvo-Freeman Real Life Scale (RFRLS), Reynell Developmental Language Scale (RDLS), and a Standardized Parental Report. Data were analyzed by the Mann-Whitney test.

  RESULTS: There were significant improvements in the language comprehension domain of WeeFIM (p=0.02), self-care caregiver assistant domain of PEDI (p=0.028), and CGI-I (p=0.003) in the LA group compared to the SLA group. As for the parental report, the LA group also showed significantly better social initiation (p=0.01), receptive language (p=0.006), motor skills (p=0.034), coordination (p=0.07), and attention span (p=0.003).

ADDITIONAL SUPPORTIVE INFORMATION

Presently, several other alternative therapies that operate on similar application and scientific method of action and operation principles as the proposed Erchonia® HLS Laser Device therapy and apply energy to the scalp region to effect improvement in the symptoms of autistic disorder are readily being evaluated through both feasibility and controlled pivotal trials. These alternative therapies also apply stimulation to the scalp region, although most are in direct contact with the scalp and provide stronger impulses and energy to the region than occurs with the Erchonia® HLS which is also not in direct contact with the scalp, with no safety issues having been reported.

Among these alternative treatment modalities, the 4 primary ones identified are the following:

1) Repetitive Transcranial Magnetic Stimulation (rTMS): rTMS is a technique used in cognitive neuroscience research as well as in therapeutic approaches in certain neurological and psychiatry diseases to affect brain activity. It consists of applying a magnetic impulse to the brain through the scalp by placing an electromagnetic coil on the surface of the scalp. The electromagnetic coil produces high current pulses that induce an electrical field in the underlying brain tissue that is proposed to modify activity of those neurons inside the magnetic field and induce an electrophysiological change in the target area. When the induced field is above a certain threshold and is directed in an appropriate orientation relative to the brain's neuronal pathways, localized axonal depolarizations are believed to be produced, thus activating the neurons in the relevant brain structure.

   Pilot studies evaluating application of rTMS to children and adolescents with both high functioning and low functioning autism have demonstrated reduction of repetitive behaviors and improved social functioning.

2) Transcranial Direct Current Stimulation (tDCS): tDCS has been evaluated through clinical trials for numerous neurological applications such as stroke, depression and schizophrenia, wherein its application has been shown to improve certain mental tasks and abilities. tDCS involves application of weak electric current to the brain through the surface of the scalp, such as through use of a 9 volt battery device.

   Improvements in various cognitive functions have been consistently demonstrated. Regarding safety, only non-significant side effects have been reported, including a mild tingling and/or itching sensation under the electrode, fatigue after treatment, headache, and insomnia; all of which typically resolve without intervention within 72 hours.

3) Acupuncture and Acupressure: Acupressure involves the stimulation of specific acupoints by firm pressure, while acupuncture involves the insertion of very fine needles into the skin at specific acupoints that may be quickly inserted and removed or left in place for some period of time.

   The therapeutic effect of acupuncture is based on stimulation at specific acupoints resulting in both local and distant effect via improving signal or modulation of electromagnetic energy

   Both acupressure and acupuncture (with or without supplemental electrical stimulation administered through attachments to the handles of the acupuncture needles – Electronic Acupuncture Treatment) have been applied to specific scalp acupoints for various neurological indications including stroke, epilepsy and depression. Improvements in cognitive and behavioral functioning have been consistently reported.

STUDY RATIONALE: Considering a positive study outcome, application of the Erchonia® HLS as proposed in this pivotal trial to reduce the severity of symptoms of autistic disorder, in particular the symptoms of irritability associated with autistic disorder, in children and adolescents aged 5 through 17 years, inclusive, may provide a simple, non-invasive, safe, effective and side-effect free alternative therapy to reduce the severity of symptoms of autistic disorder in affected children and adolescents.

STUDY DESIGN

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

TREATMENT GROUPS

Each subject will be 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 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.

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, insuring 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.

Subject Recruitment
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 Information Sheet for the child/adolescent 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 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 ensure 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 38 through 40, under the section titled: STATISICAL ANALYSIS PLAN.

STUDY PROCEDURE

STUDY TEST BATTERY

The following is information about the assessment tools that will be used in this study.

- Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision criteria (DSM-IV-TR) for autistic disorder

  American Psychiatric Association. (2000). Diagnostic criteria for autistic disorder. In Diagnostic and statistical manual of mental disorders (Fourth edition---text revision (DSM-IV-TR). Washington, DC: American Psychiatric Association, 75.

  A. A total of Six (or more) items from (1), (2), and (3), with at least two from (1), and one each from (2) and (3):

  1. Qualitative impairment in social interaction, as manifested by at least two of the following:
     - marked impairment in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction
     - failure to develop peer relationships appropriate to development level
     - a lack of spontaneous seeking to share enjoyment, interest, or achievements with other people (e.g., by a lack of showing, bringing, or pointing out objects of interest)
     - lack of social or emotional reciprocity

  2. Qualitative impairments in communication as manifested by at least one of the following:
     - delay in, or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mine)
     - in individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others
     - stereotyped and repetitive use of language or idiosyncratic language
     - lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level

  3. Restricted repetitive and stereotyped patterns of behavior, interests, and activities, as manifested by at least one of the following:
     - encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
     - apparently inflexible adherence to specific, nonfunctional routines or rituals
     - stereotypes and repetitive motor mannerisms (e.g., hand or finger flapping or twisting, or complex whole-body movements)
     - persistent preoccupation with parts of objects

  B. Delays or abnormal functioning in at least one of the following areas, with onset prior to age 3 years: (1) social interaction, (2) language as used in social communication, or (3) symbolic or imaginative play.

  C. The disturbance is not better accounted for by Rett's Disorder or Childhood Disintergrative Disorder.

➢ 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.

- 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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- ➢ Clinical Global Impressions (CGI)

The CGI is a brief 3-item observer (clinician)-rated scale that measures illness severity (CGIS), global improvement or change (CGIC) and therapeutic response. It is amongst the most widely used extant brief assessment tools in psychiatry.

The illness severity and improvement sections of the instrument are used more frequently than the therapeutic response section in both clinical and research settings.

The clinician is asked to rate the patient relative to their past 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.

Scoring:
- ✓ The CGI is rated on a 7-point scale.
- ✓ The severity of illness scale (CGI-S) uses a range of responses from 1 (normal) through 7 (amongst the most severely ill patients).
- ✓ The global improvement scale (CGI-C) scores range from 1 (very much improved) through 7 (very much worse).
- ✓ Treatment response ratings should take account of both therapeutic efficacy and treatment-related adverse events and range from 0 (marked improvement and no side-effects) and 4
- ✓ (unchanged or worse and side-effects outweigh the therapeutic effects).
- ✓ Each component of the CGI is rated separately; the instrument does not yield a global score.

References

- ✓ Leon AC, Shear MK, Klerman GL, Portera L, Rosenbaum JF, Goldenberg I. A comparison of
- ✓ symptom determinants of patient and clinician global ratings in patients with panic disorder and depression. J Clin Psychopharmacol 1993; 13(5):327–31.
- ✓ Spearing MK, Post RM, Leverich GS, Brandt D, Nolen W. Modification of the Clinical Global Impressions (CGI) Scale for use in bipolar illness (BP): the CGI-BP. Psychiatry Res 1997; 73(3):159–71.
- ✓ Zaider TI, Heimberg RG, Fresco DM, Schneier FR, Liebowitz MR. Evaluation of the clinical global impression scale among individuals with social anxiety disorder. Psychol Med 2003; 33(4):611–22.

The CGI is shown below:

1. Severity of illness
Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

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

2. Global improvement: Rate total improvement whether or not, in your judgment, it is due entirely to drug treatment.

Compared to his condition at admission to the project, how much has he changed?

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

3. Efficacy index: Rate this item on the basis of **treatment effect only**.
Select the terms which best describe the degrees of therapeutic effect and side effects and record the number in the box where the two items intersect.

EXAMPLE: Therapeutic effect is rated as 'Moderate' and side effects are judged 'Do not significantly interfere with patient's functioning'.

Therapeutic effect	**Side effects**			
	None	*Do not significantly interfere with patient's functioning*	*Significantly interferes with patient's functioning*	*Outweighs therapeutic effect*
Marked Vast improvement. Complete or nearly complete remission of all symptoms	01	02	03	04
Moderate Decided improvement. Partial remission of symptoms	05	06	07	08
Minimal Slight improvement which doesn't alter status of care of patient	09	10	11	12
Unchanged or worse	13	14	15	16

Not assessed = 00

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, 4th Edition, Text Revision criteria (DSM-IV-TR)BDI®-II
- 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 17 years
- Subject has met Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision criteria (DSM-IV-TR) 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

- Subject's caregiver agrees, and it is possible for, the subject to abstain from partaking in new treatments to treat the subject's autistic disorder symptoms during the course of 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
- Female subjects of child-bearing age are willing and able to use acceptable means of contraception throughout study participation. Acceptable means of contraception throughout study participation are: oral contraceptives (birth control pills); injectable contraceptives (such as Depo-Provera, Noristeret and Lunelle); vaginal ring (e.g. Nuva Ring); birth control patch (e.g. Ortho Evra); cervical diagrams, caps and sponges; male or female condoms; Intrauterine Devices (IUDs); Intrauterine Systems (e.g. Mirena); sterilization and abstinence.

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
- Current use of a psychotropic drug deemed effective for the treatment of aggression, tantrums or self-injurious behavior
- 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
- Subject is presently pregnant or breast feeding
- 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 change or start taking any new medications, or partake in any other new treatments, or to change the dosages they take of current medications, to treat the symptoms of autism disorder, during the course of study participation.
- Subjects must agree to notify the study investigator immediately if their treating physician makes any change to medication or dosage.
- Females of child-bearing age must agree to use acceptable means of contraception, as detailed in the study qualification evaluation section.

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 minutes.

Erchonia® HLS Treatment Administration Protocol

The treatment administration process is as follows:

1. The subject is seated comfortably.
2. The administration investigator puts on the KenTek Corporation KenTek C22-KMT-6101 light blue safety glasses.
3. The subject is correctly fitted with the KenTek Corporation KGOG-6101 light blue Medium Goggles safety goggles.
4. The Erchonia® HLS laser is applied four inches from the skin surface, and the laser light is directed perpendicular to the plain of the skin ensuring that the beam is penetrating perpendicular to the skin.
5. Pulsed laser therapy 8, 53, 73 and 101 is applied systematically to the base of the brain and temporal areas for 5 continuous minutes.
6. The HLS laser is turned off.
7. The administration investigator removes the safety glasses and the subject removes the safety goggles.
8. 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
  - 6 months for subjects who had been assigned to the active treatment group

The evaluation time points and associated measures to be evaluated during the course of this 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)

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

6 MONTHS: ACTIVE TREATMENT GROUP ONLY

Following the final enrolled subject's completion of the Week 8 Post-Treatment Evaluation, study blinding will be broken. Subjects who had been assigned to the active treatment group will take part in the 6 months post-procedure evaluation visit to gain a sense of duration of the treatment effect. At this visit, the following study measures will be recorded:

- Aberrant Behavior Checklist (ABC)
- Clinical Global Impressions (CGI)
- Medication and therapy use review
- Adverse events evaluation

PLACEBO SUBJECTS POST-STUDY CROSS-OVER OPTION

Following study unblinding, subjects who had received the placebo device will be offered the opportunity to receive the same active course of treatment as was administered to subjects who had been assigned to the active device treatment group. Subjects who wish to engage in this option will re-commence the study at the study qualification evaluation phase. Given the nature of the condition, behavioral and functional change in either direction may be expected, and as such, study qualification and baseline evaluations will be redone for this cross-over subject group, with the exception of the DSM-IV-TR diagnosis confirmed with the ADI-R as both will be current within the past 2 years as per the study inclusion qualification criteria based upon the subject's initial enrollment ion the study. Subjects will then proceed through the remainder of the course of the study as when they participated as a placebo subject and proceed to the post-procedure evaluation phase. Although these subjects and their caregivers will be aware that active treatment is being administered during this crossover phase, again by nature of the condition, the subjects are incapable of purposefully altering their behavior or function, so this will not impact the outcome of the placebo cross-over phase.

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.

Erchonia® HLS Feasibility (Pilot) Study: A feasibility (pilot) study that employed the Erchonia® HLS Laser Device with the exact same device output parameters and treatment administration protocol as proposed for the current pivotal study was completed in September, 2012.

In the pilot study, eleven (9 male and 2 female) children and adolescents aged 5 years 4 months to 16 years 10 months with autistic disorder were enrolled according to the study qualification criteria proposed for the current pivotal clinical study. All subjects received the active procedure administrations with the actual Erchonia® HLS Laser Device. The Aberrant Behavior Checklist (ABC) assessment tool was administered at Baseline evaluation (before receiving the first laser treatment administration) and at study Endpoint (after completion of the laser treatment administration protocol).

For subjects enrolled in this pilot study, the mean change from Baseline to study Endpoint in the Aberrant Behavior Checklist (ABC) Irritability Subscale score adjusted for Baseline ABC Irritability Subscale score was -9.09 (SD of change of 6.76). The mean Baseline ABC Irritability Subscale score was 14.45 (SD of 8.18) and the mean study Endpoint ABC Irritability Subscale score was 5.36 (SD of 6.70).

ANCOVA analysis for two correlated samples to evaluate the mean change from Baseline to study Endpoint in the Aberrant Behavior Checklist (ABC) Irritability Subscale score adjusted for Baseline ABC Irritability Subscale score found the mean change of -9.09 to be statistically significant at $p<0.0005$ ($F=23.27$; $p=0.00012$).

Subsequently, based on the clinically significant results from the Abilify® clinical trial combined with the pilot study results from the Erchonia® HLS study demonstrating the predicted effect size of the Erchonia® HLS Laser Device and associated treatment administration protocol for the proposed indication, the midpoint in the change on the ABC Irritability Subscale score is determined to be -8.5 points, and the clinically significant study success for the currently proposed full-scale clinical study is defined as a minimum mean difference of -8.5 points on the ABC Irritability Subscale score from Baseline to Endpoint between active and placebo treatment groups.

Therefore, the estimated 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 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

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 to be statistically significant.

- For 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.

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.

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 during the course of 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

The study Monitor will assure that the investigator is executing the protocol as outlined and intended. This includes insuring that a signed informed consent form has been attained from each subject's caregiver prior to commencing the protocol, that the study procedure protocol is administered as specified, and that all study evaluations and measurements are taken using the specified methods and correctly and fully recorded on the appropriate clinical case report forms.

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.**

TABLE OF SUBJECT EVENTS

The following table provides a progressive summary of subject events throughout the duration of this pivotal trial.

PRE-TREATMENT ACTIVITIES

STUDY QUALIFICATION

- A minor individual who attends the investigator's office for a pre-scheduled appointment pertaining to his or her ASD and/or ASD-related issues is deemed potentially suitable by the investigator for participation in the clinical study.
- The investigator discusses the possibility of participating in the study with the caregiver.
- If the caregiver is interested, the investigator presents and reviews the study informed consent form with the caregiver and reviews the information sheet with the child/adolescent.
- The caregiver voluntarily signs the study consent form.
- Subject ID is assigned.
- Subject is randomly assigned to Treatment Group.
- Study qualification inclusion/exclusion criteria evaluation is performed.

BASELINE ASSESSMENT

DEMOGRAPHICS AND TREATMENT HISTORY

- *Demographic Variables* recorded: gender, age, ethnicity
- *Medication and Treatment History*: Recording of all prescription and OTC medications used to date and therapies tried to date to treat autistic disorder or for any other indication

BASELINE EVALUATION

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

PROCEDURE ADMINISTRATION PHASE

GENERAL ASSESSMENT CONDITIONS

- Subject agrees to maintain his or her regular medication and dosage schedule to treat symptoms related to autism disorder throughout the study.
- Subject agrees to not change or start taking any new medications, or partake in any other new treatments, or to change the dosages they take of current medications, to treat the symptoms of autism disorder, during the course of study participation
- Subject agrees to notify the study investigator immediately if their treating physician makes any change to medication or dosage.
- Females of child-bearing age agree to use acceptable means of contraception throughout the study.

STUDY TREATMENT ADMINISTRATION PROTOCOL

The subject receives eight 5-minute study treatments with the Erchonia® HLS laser device: two treatments per week for 4 consecutive weeks, each treatment administration 3 to 4 days apart administered by the study investigator at the test site.

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

WEEK 4 END: Study Endpoint
- Aberrant Behavior Checklist (ABC)
- Clinical Global Impressions (CGI)

POST-TREATMENT EVALUATION PHASE

WEEK 8: Four weeks following completion of the Treatment Administration Phase:

- Aberrant Behavior Checklist (ABC)
- Clinical Global Impressions (CGI)
- Medication and therapy use review
- Adverse events evaluation

6 MONTHS: For Active Treatment Subjects Only

- Aberrant Behavior Checklist (ABC)
- Clinical Global Impressions (CGI)
- Medication and therapy use review
- Adverse events evaluation

PLACEBO SUBJECTS POST-STUDY CROSS-OVER OPTION

APPENDIX A

LETTER OF APPLICATION FOR NON-SIGNIFICANT RISK DETERMINATION

ERCHONIA CORPORATION
LETTER OF APPLICATION FOR NONSIGNIFICANT RISK DETERMINATION FOR THE ERCHONIA® HLS LASER DEVICE FOR THE TREATMENT OF IRRITABILITY ASSOCIATED WITH AUTISTIC DISORDER IN CHILDREN AND ADULTS CLINICAL STUDY V2.0 01.31.13

NAME OF THE DEVICE:
- **Model:** Erchonia® HLS Laser Device
- **Trade Name:** Spectrum by Erchonia™

INVESTIGATIONAL INDICATION: 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 irritability associated with autistic disorder in children and adolescents aged five through seventeen years, inclusive, by applying red diode (640 nm ± 10 nm) energy around the base of the skull and temporal regions for 5 minutes, 8 times across 4 weeks.

DESCRIPTION OF THE DEVICE: 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 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.

CHARGER BASE POWER SUPPLY

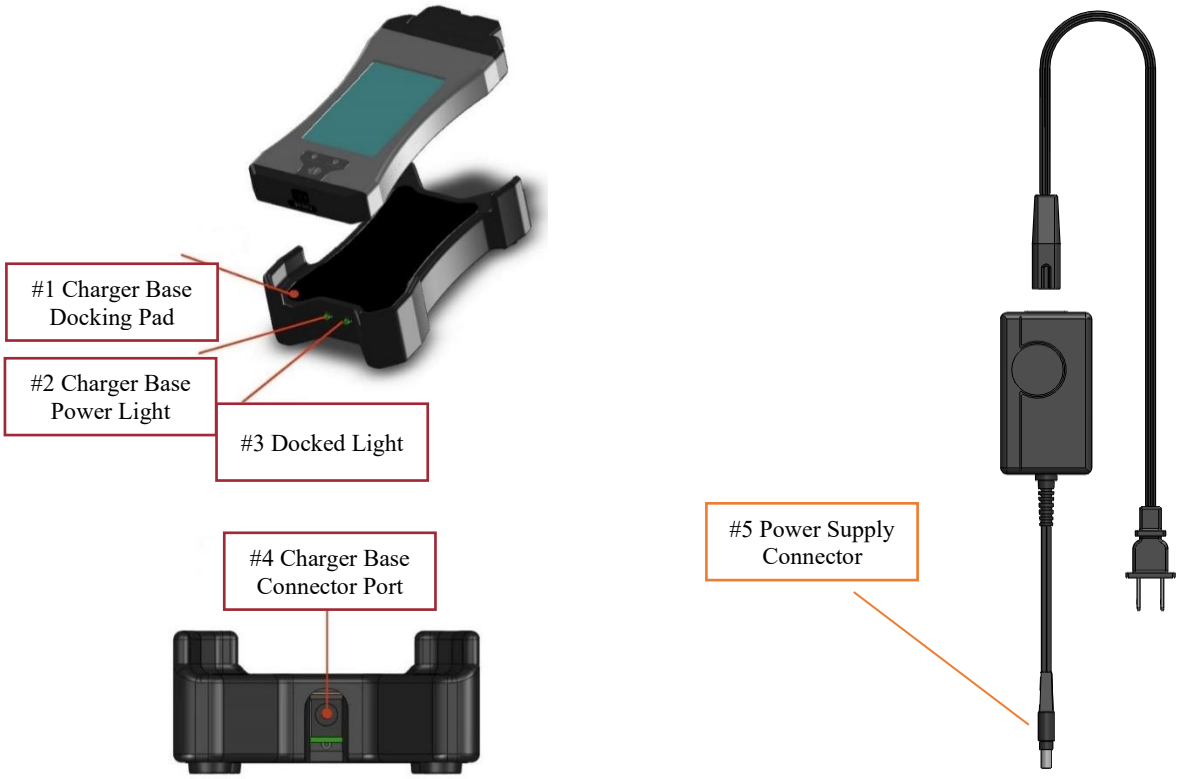

Figure 2: The Erchonia HLS Laser Charger Base and Power Supply

#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.

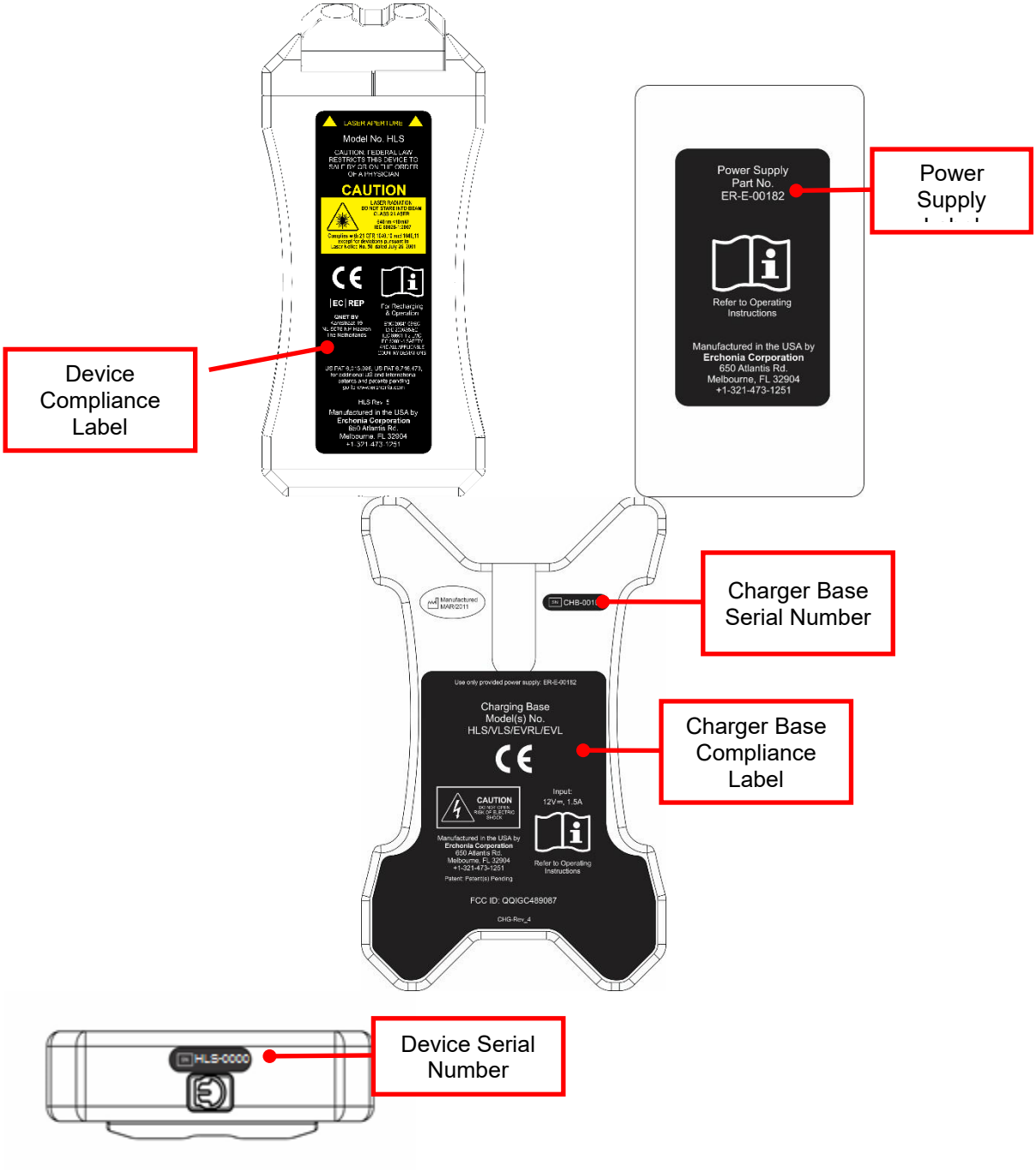

Figure 3: Erchonia HLS Laser **L**abeling

DETERMINATION OF 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 seal 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
In addition, the device used in this clinical study shall be labeled with the following NSR statement:

"CAUTION – Investigational device. Limited by United States law to Investigational use."

- Do you contend that this device as used in this protocol is an NSR device?
  _✓_ Yes ___No

- Has another IRB decided this device is SR?
  ___ Yes _✓_ No

- Does this type of device appear as SR on the FDA Information Sheet?
  ___ Yes _✓_ No

APPENDIX B

INFORMED CONSENT FORM

RESEARCH SUBJECT INFORMATION AND CONSENT FORM

TITLE:	A Double-Blind, Placebo-Controlled Randomized Evaluation of the Effect of the Erchonia® HLS Laser Device on Children and Adolescents with Autistic Disorder
PROTOCOL NO.:	Version 2.1; April 19, 2017
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 be in a research study. The purpose of this consent form is to help you decide if you want to be in the research study. Please read this form carefully. 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 all 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.

- 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 to lose any medical benefits. If you decide not to take part in this study, your doctor will continue to treat you.
- 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;
- The possible risks to you;
- 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 reduce irritability associated with autistic disorder in children and adolescents aged five through seventeen years.

PROCEDURES

- If you agree to take part in this study, you will be one of about 40 people taking part.
- This is a randomized, double-blind, placebo-controlled study. This means that if you choose to take part in this study, it will be determined by chance (like the flip of a coin) whether you 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, you have:
  - 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 you can see, so neither you nor the study investigators will be able to guess which group you are in.

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

- The study takes about six to eight months to complete, depending on whether you get the treatment with the real HLS or the fake device at the start of the study.

- 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 autistic disorder, and about medications and treatments you are doing now and have done in the past to treat the symptoms of your autistic disorder
- Get information about your other medical history, including information about other current medical conditions you may have
- Get information about other medicines you are taking or have taken in the past
- Do an interview with questions about your family, medical, developmental and education background; about your communication and social skills; and about your behavior patterns and interests
- Rate how severe your 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 autistic disorder
- Get information about your 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 all of the screening procedures, and we can confirm that you are eligible for this study.

You will need to go 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. You will sit in a chair. The laser light will shine across the bottom and sides of your head, but the laser will not touch your skin. You 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 you are taking or in the treatments you are 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 autistic disorder
- Rate how severe your autistic disorder is on a scale from 1 (normal) through 7 (amongst the most severe instances); 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); and record if there seems to be any effect of the treatment with the Erchonia® HLS Laser on your autistic disorder symptoms, or any side-effects

This should take about 15-20 minutes.

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

- Have you complete a questionnaire about the signs and symptoms of your autistic disorder
- Rate how severe your autistic disorder is on a scale from 1 (normal) through 7 (amongst the most severe instances), 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), and record if there seems to be any effect of the treatment with the Erchonia® HLS Laser on your autistic disorder symptoms, or any side-effects

This should take about 15-20 minutes.

Post-treatment Phase (Visits 10 & 11)
Four weeks after your last treatment with the Erchonia® HLS laser, you will need to come to the test site for your last visit (visit 10), where we will again:

- Have you complete a questionnaire about the signs and symptoms of your autistic disorder
- Rate how severe your autistic disorder is on a scale from 1 (normal) through 7 (amongst the most severe instances); 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); and record if there seems to be any effect of the treatment with the Erchonia® HLS Laser on your autistic disorder symptoms, or any side-effects
- Ask you if there have been any changes in the medicines you are taking or in the treatments you are doing

This should take about 20 minutes.

After everyone in the study has finished Visit 10, you will be told if you were in the group that got the real HLS or the fake Erchonia® HLS Laser treatment. If you had received the real HLS laser treatment, you will need to come to the test site six months after your last treatment for your last visit (visit 11), where we will again:

- Have you complete a questionnaire about the signs and symptoms of your autistic disorder
- Rate how severe your autistic disorder is on a scale from 1 (normal) through 7 (amongst the most severe instances); 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); and record if there seems to be any effect of the treatment with the Erchonia® HLS Laser on your autistic disorder symptoms, or any side-effects
- Ask you if there have been any changes in the medicines you are taking or in the treatments you are doing

This should take about 20 minutes.

Study Cross-Over Option

If you had received the fake laser treatment, you will be offered the chance to receive the same 8 treatments over 4 weeks as you already did, but this time with the real HLS (active) device. You do not have to take this option. If you do take this option, you will progress through the study as before with the same measures recorded.

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 you will not get any improvement in the symptoms of your autistic disorder or that they may even get worse.

Females who are pregnant or nursing a child may not take part in this study.

NEW INFORMATION

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

BENEFITS

The symptoms of your autistic disorder may lessen while you are 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 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 part in this research study.

ALTERNATIVE TREATMENT

If you decide not to enter this study, there is other care available to you, 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 be treated for the symptoms of your 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 personal and medical information. For example:

- Research records
- Records about your study visits.

Who may use and give out information about you?

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 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 you will not be used.

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

May I review or copy my 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 or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor. If you withdraw your permission, you will not be able to stay in this study.

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

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

COMPENSATION FOR INJURY
If you are injured or get 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
Your participation in this study is voluntary. You may decide not to participate, or you may leave the study at any time. Your decision will not result in any penalty or loss of benefits to which you are entitled.

Your 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 best interest;
- you do not consent to continue in the study after being told of changes in the research that may affect you;
- or for any other reason

If you leave the study before the planned final visit, you may be asked by the study doctor to have some of the end of study procedures done.

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

If you have questions about your rights as a research subject or if you have questions, concerns or if you have questions about your 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 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 part in it have been answered. I freely consent to be in this research study.

I authorize the use and disclosure of my 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 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 [7] - [17]:

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 and Adolescents with Autistic Disorder
PROTOCOL NO.:	Version 2.1; April 19, 2017
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 months or ten months. You will have to come to the study center eleven or twenty-one 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 you didn't get the real treatment the first time, you can choose to have the real treatment afterwards, if you like. You do not have to choose this.

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 you are a girl and have started your periods, pregnancy testing will be done. You must use birth control or not have sex during the study. This is because the Erchonia® HLS Laser device has not been tested on pregnant woman and could cause birth defects in babies. You must not take part in this study if you become pregnant. If at any time you think you might be pregnant, you must tell your study doctor right away.

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 #>.

RESEARCH SUBJECT INFORMATION SHEET FOR ADOLESCENTS:

TITLE: A Double-Blind, Placebo-Controlled Randomized Evaluation of the Effect of the Erchonia® HLS Laser Device on Children and Adolescents with Autistic Disorder

PROTOCOL NO.: Version 2.1; April 19, 2017

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 participate in a clinical research study. Your decision to be in this study is voluntary. You do not have to participate in this study if you do not want to.

This information sheet will give you information about the risks and benefits of this study so that you can make a better decision about whether you want to take part or not.

PURPOSE OF THE STUDY

The purpose of this research study is to see if using the Erchonia® HLS Laser device can help to lessen irritability associated with autistic disorder in children and adolescents. You are being asked to be in this study because you have autistic disorder.

In this study, you will receive eight treatments with the Erchonia® HLS Laser device over four weeks. If you don't receive the first eight treatments with the real Erchonia® HLS Laser, you may choose to get another eight treatments with the real laser.

PROCEDURES

You will be in this study for about eight or ten months.

You will have eleven or twenty-one visits.

Procedures done during this study include a history, an interview, and a questionnaire.

RISKS AND DISCOMFORTS

There have not been any side effects reported with use of the Erchonia® HLS Laser device.

There may be risks with using the Erchonia® HLS Laser device that are not yet known. Additional side effects that are unknown at this time and could occur during treatment include skin irritation and itching, change in skin color, skin rash, marks on the skin, pain/discomfort and infection.

It is possible that your autistic disorder symptoms will not get any better or that they may even get worse.

The effects of using the Erchonia® HLS Laser device during pregnancy have not been well studied. Therefore, there may be unknown risks to the unborn child if you become pregnant during this study. Due to these potential risks you must not participate in this study if you become pregnant, plan to become pregnant during the research study period, or are breast-feeding a child. Pregnancy testing will be done during the study and an acceptable form of birth control (including no sexual intercourse) must be used during the study.

POSSIBLE BENEFITS OF THE STUDY

The symptoms of your autistic disorder may improve as a result of your participation in this study. However, this cannot be guaranteed. You may not experience any direct health benefits. Information from this study may lead to a better treatment in the future for adolescents and children with autistic disorder.

For further information about this study, please refer to the consent form discussed with you for this study.

CONSENT

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

I authorize the use and disclosure of my 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 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 [7] - [17]:
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 — Da