Erchonia® EVRL

A Placebo-Controlled, Randomized evaluation of the effect of the Erchonia® EVRL, manufactured by Erchonia Corporation (the Sponsor), for prescription home use application in providing temporary relief from diabetic neuropathy foot pain.

Version 2.0
January 20, 2022

Appendix B: Clinical Efficacy Testing

Revision #	Description of Changes	Approved by:	Date
1.0	Original Protocol submitted for Q-Sub	Travis Sammons	September 9, 2021
2.0	Changes were made to accommodate satisfaction of Q-sub Q211922. Intended Use of device changed from OTC to Prescription Home Use.	Travis Sammons	January 20, 2022

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STUDY INFORMATION

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PURPOSE OF STUDY
The purpose of this clinical study is to determine the effectiveness of the Erchonia® EVRL, manufactured by Erchonia Corporation (the Company), in providing prescription home use application for temporary relief of diabetic neuropathy foot pain in individuals diagnosed with diabetic neuropathy by a suitably qualified and licensed health professional.

EXPECTED RESULTS
Following completion of the study treatment administration protocol with the Erchonia® EVRL, it is anticipated that compared to baseline, at least 35% more subjects in the test group than in the placebo group will show a 30% or greater reduction in self-reported VAS pain rating in the feet at study endpoint evaluation relative to baseline.

STUDY DESIGN
This clinical study is a prospective, double blind, placebo-controlled, randomized design evaluation of the effect of the Erchonia® EVRL for prescription home use application in providing temporary relief of diabetic neuropathy foot pain.

SUBJECT GROUPS
Subjects enrolled in the clinical study will not have been enrolled in the Human Factors Validation Testing study.

Each enrolled subject will be randomized to the active treatment group or to the placebo treatment group of the clinical study, as follows:

Active treatment group: Subjects randomized to the active treatment group will self-administer the study treatments with the active (true) Erchonia® EVRL laser in his or her own home.

Placebo treatment group: Subjects randomized to the placebo treatment group will self-administer the study procedures with a 'fake' (placebo) Erchonia® EVRL laser in his or her own home.
The 'fake' (placebo) laser device will appear to the subject to be an active device but will not produce any therapeutic light output. The placebo laser device is designed to have the same physical appearance as the actual (active) laser device, including the appearance of any visible and invisible light output. Therefore, both the active and placebo devices emit light when activated that is indistinguishable to the subject. As the laser light does not put out any notable degree of heat or noise, these are also not distinguishing factors for subjects between the active and placebo devices.

Regardless of whether the subject self-administers the study treatments with the actual or the fake laser device, all subjects will be required to adhere to all phases of the entire protocol design.

DOUBLE BLIND DESIGN

This clinical study is a double-blind design, such that neither the subject nor the investigator is aware of whether the subject has been provided with the active or the placebo Erchonia® EVRL device. Unblinding will occur after the final data set has been fully analyzed

The blinding procedure is as follows:

1) Each subject is randomly assigned to Treatment Group A or to Treatment Group B. Subjects assigned to Treatment Group A will receive the Erchonia® EVRL A and subjects assigned to Treatment Group B will receive the Erchonia® EVRL B. Only one individual employee at the study Sponsor site will know which label ('A' or 'B') corresponds to the actual (active) EVRL device and which label corresponds to the 'fake' device until the final study data set analysis is complete. That individual will ensure that this information is stored and maintained confidentially at the Sponsor's work site.
2) The fake (placebo) Erchonia® EVRL is designed to have the same physical appearance as the actual Erchonia® EVRL, including the appearance of any visible and invisible light output. Therefore, both the test and placebo devices 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 between the two groups.

RANDOMIZATION

Subject randomization occurs following attainment of subject consent. Subject allocation to treatment group will be via variable block randomization with varying block sizes of two, four and six used at random to minimize the likelihood of predicting the next treatment group assignment.

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

Concealment will be insured as follows:

(ii) Each computer-generated randomization sequence is unique and will therefore not be able to be replicated.
(iii) Randomization will occur to either 'Treatment Group A' or to 'Treatment Group B' rather than to a test or placebo group, and only one designated individual at the Sponsor site will know which assignment (A or B) corresponds to the active device and which corresponds to the fake device. Unblinding will not occur until the final study data set analysis is complete.

SUBJECTS

<u>Recruitment</u>

Subjects will be recruited from online advertisements for individuals who have been previously diagnosed with diabetes induced peripheral neuropathy by a suitably qualified and licensed health professional.

<u>Compensation</u>

A subject who completes his or her participation in this clinical study through to the final post-treatment administration will receive financial compensation of $200.

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

Sample size
There will be 64 qualified subjects enrolled in this clinical study:

32 subjects in the active treatment group
32 subjects in the po treatment group

Rationale for sample size
Based on the following parameters established for the purposes of assessing efficacy of the Erchonia® EVRL in this clinical study …:

- Individual subject success criteria defined as a 30% or greater reduction in self-reported Degree of Pain rating on the 0-100 VAS from baseline to study endpoint evaluation.

  N.B.: The clinical relevance of a 30% change in VAS score is explained and supported in the STATISTICAL ANALYSIS PLAN section further along in this protocol document.

- Overall study success criteria of at least a 35% difference between the active device group and the placebo device group, comparing the proportion of individual successes in each group.
- It is anticipated that about 55% of subjects in the active device group and about 20% of subjects in the placebo device group will meet the individual success criteria, and
- intended application of a two-tailed test with an alpha value of 0.05 and Power of 0.8

  …the sample size of 29 subjects per group (active group and placebo group, separately) has been determined using the following reference calculator: *Hypothesis Testing: Categorical Data - Estimation of Sample Size and Power for Comparing Two Binomial Proportions* in Bernard Rosner's *Fundamentals of Biostatistics.*

For the purposes of sample size calculation, it is anticipated that about one-twentieth of subjects overall may withdraw 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 group:

Final sample size = sample size X 1/(1-d); where d = # expected dropouts/# subjects enrolled.
Final sample size = 29 X 1/(1-0.083)
Final sample size = 29 X 1/0.917 = 29 X 1.0905 = 31.62, rounded to 32 subjects per treatment group.

Therefore, a minimum starting sample size of 32 subjects in each treatment group is needed to ensure that sufficient numbers remains at the end of the trial (29 subjects per group) for any significant differences found between groups to be considered statistically valid and representative of the general population being sampled. This results in a total of 64 subjects being enrolled in this study across both study treatment groups.

STUDY PROCEDURE

STUDY TEST BATTERY

The following are the study assessment tools to be used and the variables to be recorded in this clinical study.

BASELINE VARIABLES

A. Neuropathy Variables

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

B. Medication and Treatment

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

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

OUTCOME ASSESSMENT TOOLS

PRIMARY OUTCOME MEASURE:

VISUAL ANALOG SCALE (VAS) DEGREE OF PAIN RATING: Subjects will be asked to rate the overall degree of pain experienced in their feet on the following 0-100 mm (0 -10 cm) Visual Analog Pain Scale, by responding to the following question:

"Using the scale below, please mark with a cross (X) the spot along the 0 to 100 line below that best shows **how much pain you feel in your feet** right now. '0' means you feel no pain at all and '100' means you feel the worst pain imaginable. **Please mark only one spot. Do not think of or write in a number**."

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

Like a thermometer, this means that its two ends are rooted, and a doubling of the score does accurately reflect a doubling of the pain. Consequently, sensitive t-tests and ANOVA methods can

be used in the analysis, so that significant differences can be identified with relatively small sample sizes or small differences between groups.
Source: Measuring Pain by Adrian White, Acupuncture in Medicine, November 1998 – Vol 16 No. 2

To participate in the study the subject agrees to refrain from consuming any pain relief medication within 6 hours of recording a required VAS Degree of Pain Rating to ensure that the effect of the pain relief medication does not influence any potential treatment effect of the study treatment with the Erchonia® EVRL as evidenced through the VAS ratings.

SECONDARY OUTCOME MEASURES

NEUROPATHIC PAIN SYMPTOM INVENTORY (NPSI): The NPSI was developed in 2004 by Bouhassira Didier to evaluate the different symptoms of neuropathic pain in adults. It is a 12-item self-administered patient-reported outcome (PRO) assessment tool with a recall/ observation period of over the past 24 hours. It contains 10 descriptors representing 5 distinct dimensions on the basis of factor analysis: burning pain, deep pain, paroxysmal pain, evoked pain, paresthesia/dysesthesia, and 2 temporal items designed to assess pain duration and the number of pain paroxysms. The NPSI has been validated in patients with definite neuropathic pain of peripheral or central origin.

The development and validation of the NPSI is contained in the abstract below:

Development and validation of the Neuropathic Pain Symptom Inventory.
Bouhassira D, Attal N, Fermanian J, Alchaar H, Gautron M, Masquelier E, Rostaing S, Lanteri-Minet M, Collin E, Grisart J, Boureau F.
Pain. 2004 Apr;108(3):248-57.

This study describes the development and validation of the Neuropathic Pain Symptom Inventory (NPSI), a new self-questionnaire specifically designed to evaluate the different symptoms of neuropathic pain. Following a development phase and a pilot study, we generated a list of descriptors reflecting spontaneous ongoing or paroxysmal pain, evoked pain (i.e. mechanical and thermal allodynia/hyperalgesia) and dysesthesia/paresthesia. Each of these items was quantified on a (0-10) numerical scale. The validation procedure was performed in 176 consecutive patients with neuropathic pain of peripheral (n = 120) or central (n = 56) origin, recruited in five pain centers in France and Belgium. It included: (i) assessment of the test-retest reliability of each item, (ii) determination of the factorial structure of the questionnaire and analysis of convergent and divergent validities (i.e. construct validity), and (iii) evaluation of the ability of the NPSI to detect the effects of treatment (i.e. sensitivity to change). The final version of the NPSI includes 10 descriptors (plus two temporal items) that allow discrimination and quantification of five distinct clinically relevant dimensions of neuropathic pain syndromes and that are sensitive to treatment. The psychometric properties of the NPSI suggest that it might be used to characterize subgroups of neuropathic pain patients and verify whether they respond differentially to various pharmacological agents or other therapeutic interventions.
PMID: 15030944

The full article and the NPSI Assessment tool are contained in **Appendix K** of this clinical study protocol.

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

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

BLINDING EFFICACY EVALUATION TOOLS

Subject Perceived Group Allocation and Rationale
The subject records whether he or she believes to have received the study treatments with the true or fake Erchonia® EVRL and records verbatim his or her reasoning or rationale for this perceived determination.

STUDY PROCEDURE PROTOCOL

STUDY QUALIFICATION

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

ASSIGNMENT OF SUBJECT IDENTIFICATION NUMBER
The subject is assigned to 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 RANDOMIZATION TO TREATMENT GROUP
Following signing of the consent form and prior to study qualification evaluation, a subject is randomly assigned to Treatment Group A or to Treatment Group B, following the methodology outlined above in the STUDY DESIGN section of the protocol.

STUDY QUALIFICATION CHECKLIST
To be eligible for study participation, a subject must satisfy the following qualification criteria:

INCLUSION CRITERIA

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

- Previously diagnosed with diabetes induced peripheral neuropathy by a suitably qualified and licensed health professional within the past 6 months.

- Over the age of 18 years.
- Able to read and write English.
- Constant feet pain on-going over at least the past 3 months.
- If using analgesics (pain medication), must be on a stable analgesic regimen (i.e., no changes to the prescribed analgesic regimen) over a period of at least 14 days prior to enrollment; and willing and able to not have planned upward dose titration of analgesics during the study period. The subject may elect to decrease analgesic use during the study. Cannabis prescribed for medicinal purposes would qualify as an analgesic in this context.
- Willing and able to refrain from engaging in any non-study procedure therapies for the management of foot pain throughout the course of study participation, including conventional therapies such as physical therapy, occupational therapy and hot or cold packs, as well as alternative therapies such as chiropractic care and acupuncture.
- Agrees to refrain from taking a dosage of analgesic (pain medication) for at least 6 hours before a scheduled VAS foot pain rating is to be recorded.
- Subjects' degree of foot pain on the 0-100 VAS, with "0" being no pain and "100" being worst pain imaginable, is 50 or greater.

EXCLUSION CRITERIA

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

- Pregnant or think they might be pregnant.
- Open wounds (sores, cuts, ulcers, etc.) around the feet
- Cancerous growths around the feet.
- Difficulty with hand dexterity sufficient to impact ability to administer treatments with the laser such as from severe arthritis in the hands, Multiple Sclerosis, Cerebral Palsy, Parkinson's Disease, Huntington's Disease, etc.

PRE-TREATMENT EVALUATION PHASE

The pre-treatment evaluation phase commences following successful study qualification.

BASELINE VARIABLES

- Baseline Foot Variables
- Medication and Treatment
- Insulin Dependency
- Subject Demographics

PRE-TREATMENT OUTCOME ASSESSMENTS

- Visual Analog Scale (VAS) Degree of Foot Pain Rating
- Neuropathic Pain Symptom Inventory (NPSI)

The Pre-Treatment Outcome assessments will serve as the Baseline data set.

AT-HOME TREATMENT ADMINISTRATION PHASE

A fully qualified enrolled subject will be provided either a Erchonia® EVRL A or B device based on his or her randomization to treatment group (see Randomization). Additionally, the enrolled subject will be provided the EVRL Proper Use Reference Guide **(Appendix D)** and applicable Case Report Forms **(Appendix M)** for capturing study outcome assessments.

TREATMENT ADMINISTRATION PROTOCOL

- The treatment administration phase extends over 3 consecutive weeks.
- The subject self-administers two treatment administrations with the Erchonia® EVRL (A or B) on each consecutive day of the 3-week treatment administration phase for a total of 42 self-administered treatments.
- Each treatment administration lasts 5 minutes per foot, for a total of 10 minutes.
- Each treatment is self-administered by the subject in his or her own home.

TREATMENT ADMINISTRATION PHASE MEASURES

The following treatment administration phase measures will be recorded by the subject at home through the provided Case Report Forms **(Appendix M)**.

10 DAY EVALUATION

Following 10 days of study treatment administrations (20 treatment administrations) with the Erchonia® EVRL (approximately halfway through the treatment administration phase), the following will be recorded on the provided case report forms by the subject at home.

- Visual Analog Pain Scale (VAS) Degree of Foot Pain Rating

3 WEEK EVALUATION: STUDY ENDPOINT

Following completion of the entire 3 weeks of study treatment administrations with the Erchonia® EVRL, the following will be recorded on the provided case report forms by the subject at home as outlined in the STUDY TEST BATTERY section above. These recordings will form the study endpoint data set from which change from baseline will be evaluated with respect to assessing study outcome

- Visual Analog Pain Scale (VAS) Degree of Foot Pain Rating
- Neuropathic Pain Symptom Inventory (NPSI)
- Subject Satisfaction With Study Outcome
- Perceived Treatment Group

POST-TREATMENT ACTIVITIES

7 WEEK EVALUATION: 4 Weeks Post-Treatment

Four weeks following the completion of the 3-week treatment administration phase, the following will be recorded on the provided case report forms by the subject at home, as outlined in the STUDY TEST BATTERY section above.

- Visual Analog Pain Scale (VAS) Degree of Foot Pain Rating
- Neuropathic Pain Symptom Inventory (NPSI)
- Subject Satisfaction With Study Outcome
- Perceived Treatment Group

COMPLIANCE ASSESSMENT LOG
The subject will record each day when they have administered a treatment with the Erchonia® EVRL Laser.

CHANGE IN MEDICATION RECORD SHEET
If at any time during the treatment and/or post-treatment administration phases the subject has a change in his or her medication use (cessation of prior medication, change in dosage/frequency of use of a current medication, addition of a new medication) the subject will record the medication name, dose/frequency of use, expected duration of medication use, and the reason for the change in the Change in Medication Record Sheet.

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

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

Copies of all subject case report forms will be made and supplied to the study statistician and Erchonia Corporation who will each maintain these copies in a separate clinical study file that is kept in a locked filing cabinet on their respective premises. The original records will be maintained at the respective test sites.

Subjects' identities will be kept confidential by assigning each subject a unique de-identified subject ID upon acceptance into the study. The subject ID will comprise the investigator's two initials (first and last name initials) and a three-digit number that will be based upon the subject's order of entry into the clinical study. For example, under Study Investigator John Black, the third subject enrolled in the study would have a subject ID of JB003.

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

STATISTICAL ANALYSIS

STUDY ANALYSIS POPULATIONS

(i) Intent-to-Treat (ITT) Population

The Intent-to-Treat (ITT) analysis population is defined as all consented and enrolled subjects. The ITT population will comprise the principal population analysis for evaluation of study primary efficacy outcome.

(ii) Per Protocol Population

The per protocol analysis population is defined as all consented and enrolled subjects who completed the entire clinical study per protocol, inclusive of all treatment administrations and all study activities and assessments per protocol without missing data or major protocol deviations. The per protocol population will comprise the secondary population analysis of the study primary efficacy outcome to provide support for the principal ITT population analysis as well as for all secondary outcome assessments.

HANDLING OF MISSING DATA

Based on over twenty-five (25) years of experience conducting comparable clinical trials through the study Sponsor, Erchonia Corporation, the relatively small sample size, the short duration of the trial, and the minimal requirements and commitments required from enrolled subjects, it is anticipated that withdrawal and lost-to-follow-up rates will be minimal and so will be missing data. Therefore, the single imputation methodology is selected as that to be implemented to account for any missing data. Single imputation methodology is applicable to impute missing values when a dataset is small, the number of missing values is small, the missing data is assumed to be Missing Completely at Random (MCAR), and outcome analysis procedures are simple. The single imputation methodology selected for this study is whichever is more conservative of the mean or the median of the variable for the treatment group from which the missing data emanated.

BASELINE RECORDINGS

SAMPLE DEMOGRAPHICS

Sample demographics recorded at Baseline assessment will be summarized descriptively by treatment group, using mean, standard deviation, median and range (minimum, maximum) for the continuous variable of subject age in years, and by number (N) and percentage (%) for the categorical sample variables of gender and ethnicity. Sample demographics will be compared for differences between treatment groups and test sites. Any identified differences will be explored with respect to potential impact on study outcome.

NEUROPATHY VARIABLES

Sample neuropathy continuous variables recorded at Baseline assessment of months since diagnosis of diabetes, and months since onset of peripheral neuropathy foot pain will be summarized descriptively by treatment group, using mean, standard deviation, median and range (minimum, maximum). The categorical Baseline neuropathy variable of presence or absence of insulin dependency will be summarized descriptively by number (N) and percentage (%) per category. Sample demographics will be compared for differences between treatment groups and test sites. Any identified differences will be explored with respect to potential impact on study outcome.

MEDICATION AND TREATMENT

The below medication and treatment usage as recorded at Baseline assessment will be summarized categorically by, and compared between, treatment groups using number (N) and percentage (%):
(i) Current medications taken for relief of diabetic foot pain
(ii) Prior treatment approaches for relief of diabetic foot pain
(iii) Concomitant medication and therapy use: non-pain relief indications

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

Primary efficacy outcome measure for this clinical study will be a statistically significant difference in the proportion of subjects between active and placebo treatment groups who achieve a clinically meaningful and statistically significant decrease in self-reported VAS pain rating from Baseline (pre-treatment) to study Endpoint (Week 3).

The principal primary efficacy outcome evaluation will be performed for the study intent-to-treat (ITT) population according to the following pre-determined primary efficacy success criteria.

Individual Subject Success Criteria
Individual subject success criteria is defined as a 30% or greater decrease (≥30%) in self-reported pain rating on the 0 to 100 Visual Analog Scale (VAS) at study Endpoint (Week 3) relative to Baseline.

Overall Study Success Criteria.
Overall study success criteria defined as at least a 35% difference between treatment groups, comparing the proportion of individual successes in each group. It is anticipated that about 55% of subjects in the active treatment group will meet the individual success criteria and about 20% of subjects in the placebo treatment group will meet the individual success criteria.

The clinical relevance of a 30% change in VAS score has been well established by FDA's Division of Physical Medicine and Rehabilitation Devices. The following Erchonia Corporation light therapy devices (Product Code NHN) obtained FDA 510(k) clearance based on clinical trials employing the 30% VAS change as the primary efficacy endpoint for pain reduction:

1. K221987; 09/01/22: "Erchonia® GVL: is indicated while using the green and violet diode simultaneously, for adjunctive use in providing temporary relief of minor chronic neck and shoulder pain of musculoskeletal origin."

2. K191257; 08/08/19: "Erchonia® EVRL: is indicated while using the red and violet diode simultaneously, for adjunctive use in providing temporary relief of minor chronic neck and shoulder pain of musculoskeletal origin."

2. K180197; 5/21/18; "Erchonia® FX-635: is indicated for the following two indications:
   a. as an adjunct to provide relief of minor chronic low back pain of musculoskeletal origin.
   b. as an adjunct to reducing chronic heel pain arising from plantar fasciitis."

3. K132940; 04/14/14: "The Erchonia Allay laser is indicated as an adjunct to reducing chronic hell pain arising from plantar fasciitis."

4. K012580; 01/17/02: "The TUCO Erchonia PL2000 is indicated for adjunctive use in providing temporary relief of minor chronic neck and shoulder pain of musculoskeletal origin."

Evaluation Time Point
The study end evaluation time point at which primary study success will be analyzed is at three weeks post-baseline, following completion of the 42nd and final study treatment administration with the Erchonia® EVRL.

Hypotheses
The pre-established null and alternative hypotheses for the primary efficacy outcome evaluation were the following:

(i) Null Hypothesis: The difference in the proportion of individual subject successes between the active and placebo treatment groups will be less than 35%.

H_o: μA - μP < 35%

Where 'A' = active treatment group; and 'P' = placebo treatment group

(ii) Alternative Hypothesis: The difference in the proportion of individual successes between the active and placebo treatment groups will be 35% or greater in favor of the active treatment group.

H_1: μA - μP ≥ 35%

Where 'A' = active treatment group; and 'P' = placebo treatment group

(i) Responder Rate Analysis

Principal determination of study primary outcome success as defined will be according to Responder Rate Analysis calculated by determining the percentage of individual subject successes in each of the active and placebo treatment groups, separately, and then subtracting the two proportions to attain the difference in proportions between the two treatment groups. Overall Study Success will be demonstrated if this difference is ≥35% in favor of the higher proportion occurring for the active treatment group.

(ii) Chi-Squared Analysis of Proportions

A chi-squared analysis to assess the significance of the difference in the proportion of individual subject successes (Responder Rate) between the active and placebo treatment groups will be performed. A two-tailed significance level of 5% will be considered statistically significant.

(iii) ANCOVA of Mean Change in Diabetic Peripheral Neuropathy Foot Pain VAS Ratings

Parametric Analysis of Covariance (ANCOVA) with the mean change from Baseline to study Endpoint (Week 3) in diabetic peripheral neuropathy foot pain ratings on the 0-100 VAS as the dependent variable, treatment group as the independent variable of interest, and Baseline diabetic peripheral foot pain VAS rating as a covariate will be performed. A two-tailed significance level of 5% was predetermined to be considered statistically significant.

SECONDARY EFFICACY OUTCOMES

The following secondary efficacy outcomes will be evaluated to provide support for the primary efficacy outcome analysis. **As no claims are intended to be made based on the secondary efficacy outcome evaluations, secondary efficacy outcome analysis will be performed for the per protocol analysis population only and statistical analyses will not be performed; secondary efficacy outcomes data will be presented descriptively only.**

(i) Diabetic Peripheral Neuropathy Foot Pain VAS Ratings Across Study Progression

Descriptives of mean, standard deviation (SD), median, and range (minimum, maximum) will be presented in a table for the degree of pain ratings recorded on the 0-100 VAS for diabetic peripheral neuropathy pain at each of the four (4) study assessments of Baseline (pre-treatment), Day 10 (Post-Baseline), Endpoint (3 Weeks Post-Baseline), and Follow-Up (7 Weeks Post-Baseline - 4 Weeks Post-Treatment End) by treatment group.

(ii) Neuropathic Pain Symptom Inventory (NPSI) Scores Across Study Progression

Descriptives of the mean, standard deviation (SD), median and range (minimum, maximum) for each of the five (5) dimension scores on the NPSI and the Total NPSI score will be presented in a table for each of the three study assessments of Baseline, Endpoint (Week 3), and Follow-Up (Week 7) by treatment group.

SATISFACTION WITH STUDY OUTCOME RATINGS

Subject satisfaction scores will be presented descriptively in a table as number (N) and percentage (%) per response category (Very Satisfied, Somewhat Satisfied, Neither Satisfied nor Dissatisfied, Not Very Satisfied, Not at All Satisfied) at each assessment of Study Endpoint (Week 3) and Study Follow-Up (Week 7) by treatment group.

Ratings will be further categorized into ‘positive satisfaction responses’ by summing the ‘very satisfied’ and ‘somewhat satisfied’ categories. The proportion of ‘positive satisfaction responses’ in each category at each assessment visit between treatment groups will be compared using a chi-squared analysis with a two-tailed significance level of 5% considered statistically significant.

Additionally, Spearman’s correlation analysis will be conducted to assess the relationship between subject satisfaction with treatment outcome ratings and mean change in subject VAS ratings for diabetic peripheral neuropathy foot pain from Baseline to study Endpoint (Week 3), and from Baseline to Follow-Up (Week 7) assessments.

CHANGES IN MEDICATION USE AND TREATMENT COMPLIANCE

Subject compliance with treatment administration and maintenance of medication use reported at baseline without change across study duration will be assessed and reported descriptively based on subject recordings on the Subject Daily Diary.

BLINDING EFFICACY EVALUATION

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

Statistical evaluation of blinding efficacy will be performed as follows:

(i) The number (N) and percentage (%) of subjects who correctly perceived their treatment group assignment and the percentage of subjects who did not correctly perceive their treatment group assignment will be calculated for each treatment group.

(ii) A **Chi-Squared Analysis** to assess the significance of the difference in the proportion of subjects who accurately perceived their Baseline treatment group assignment between the active and placebo treatment groups at each of Endpoint (Week 3) and Follow-Up (Week 7) assessments will be performed. A two-tailed significance level of 5% will be considered statistically significant.

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

- *Positive blinding efficacy* will be supported through qualitative assessment of comments provided to support perceived group assignment that pertain to the determination being based on treatment efficacy or lack thereof, e.g.: 'My foot pain is much less than it used to be, so I believe I got the real treatment' or 'My foot pain hasn't really changed, so I believe I got the fake treatment.'

- *Blinding will be determined to have failed* if comments provided to support perceived group assignment pertain to factors such as sensation/visual clues or overhearing conversations by research staff members.

INDIVIDUAL SUBJECT VAS RATINGS ACROSS STUDY DURATION
Individual subject data for the Primary Outcome Measure of diabetic peripheral neuropathy foot pain VAS Ratings as recorded at each of Baseline (pre-treatment) and Study Endpoint (Week 3) assessments, by Treatment Group, by Test Site, will be presented in table format.

INDIVIDUAL TEST SITE DATA
Key demographic and neuropathy variables and the primary outcome assessment for the ITT analysis population will be presented by treatment group by each of the four individual test sites participating in this study. Data will be presented in descriptive format only due to the small sample sizes that preclude statistical conclusions from being validly drawn.

SAFETY ANALYSES
Safety analyses will be based on all subjects who were randomized to the test or to the placebo treatment group. 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 between test and placebo treatment group subjects.

INFORMED CONSENT
- Informed consent will be an agreement between the individual investigator and each subject, having the capacity to understand and make an informed decision. Consent will be obtained prior to each potential subject's participation in this clinical study.

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

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

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 M.**

END OF DOCUMENT

RESEARCH SUBJECT INFORMATION AND CONSENT FORM

TITLE: A placebo-controlled, randomized, double-blind evaluation of the effect of the Erchonia® EVRL™ for prescription home use application in providing temporary relief from diabetic peripheral neuropathy foot pain.

PROTOCOL NO.: R-DPN
WIRB® Protocol #

SPONSOR: Erchonia Corporation

INVESTIGATOR:

STUDY-RELATED PHONE NUMBER(S):

This consent form is being provided to you and may be discussed with family or friends before making your decision. This consent form may contain words that you do not understand. Please ask the study investigator in person, or during a teleconference or videoconference to explain any words or information that you do not clearly understand.

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 investigator explain the research study to you,
- Asking questions about anything that is not clear.

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.
- 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, is studying the use of a device called the Erchonia® EVRL™ that gives off low level laser light. This study is to see if using the Erchonia® EVRL™ can help to relieve the chronic pain arising from diabetic peripheral neuropathy. The use of the Erchonia® EVRL™ in this study is investigational, as the EVRL™ has not been cleared for market by the FDA for relieving pain associated with neuropathy foot pain.

PROCEDURES

- If you agree to take part in this study, you will be one of about 64 people taking part.
- This is a randomized, 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 placebo treatments.

  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

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 you will be able to guess which group you are in.

If you are currently utilizing prescribed pain medicine, to take part in this study you must agree to not make changes to current prescribed analgesic regimen, however you may elect to decrease the pain medication use during the study.

- The study takes about 7 weeks to complete.
- The study process is as follows:

SCREENING
If you are interested in taking part in this research study, we will conduct in office visit or a remote call to determine if you are eligible for the study. The office visit or screening call will last 10-15 minutes.

PRE-PROCEDURE EVALUATION PHASE
On the same day as the screening, if you are eligible for the study, we will ask you to:

- provide information about your neuropathy pain and about treatments you may have tried to relieve your foot pain associated with diabetic neuropathy.
- provide information on any medication you may currently be taking.
- rate how painful your foot pain is to you at that time on a scale from 0 to 100, where '0' means 'no pain' and '100' means 'worst pain imaginable.'
- fill out a questionnaire about different symptoms of your foot pain
- provide information about your age, gender, and ethnicity.

The pre-procedure evaluation takes about 15 minutes to complete.

AT-HOME TREATMENT PHASE (3 WEEKS)
The at-home study treatment phase will start once you have successfully completed the screening and pre-procedure evaluation. The at-home study treatment phase will last 3 weeks. The process you will go through during the at-home treatment phase is as follows:

- You will be shipped a Erchonia EVRL™ laser and operation manual (instructions for use).
- You will need to administer treatments with the Erchonia EVRL™ during the at-home treatment phase by following the instructions contained in the Proper Use and Reference Guide.
- You will need to administer the treatments with the Erchonia EVRL™, twice a day for 3 weeks (42 total treatments). Each treatment is applied 5 minutes per foot for a total of 10 minutes.

- You will need to record each time you administer a treatment.
- You cannot do any other treatments to help with your foot pain during the at-home study treatment phase.

TREATMENT PHASEAT HOME EVALUATION FORMS (DAY 10, DAY 21)

There are two at home evaluation forms you must complete during the 3 Week study treatment phase:

1) at the end of the first 10 days of the treatment phase, and;
2) at the end of the 3-week treatment phase.

At each of these two evaluation points, you must refrain from taking any pain medicine at least 6 hours prior to completing the evaluation forms. The forms will ask you to:

- rate how painful your foot pain is to you at that time on a scale from 0 to 100, where '0' means 'no pain' and '100' means 'worst pain imaginable.'

The 3-week evaluation form will also ask you to:

- fill out a questionnaire about different symptoms of your foot pain
- rate how satisfied you are with the outcome of the treatment administration with the Erchonia® EVRL™ Laser on a five-point scale.
- record whether you believe you received treatments with the actual EVRL™ laser or the fake EVRL ™ device and why you think this.

Each of the two evaluation forms take about 5-10 minutes to complete.

ADDITIONALLY, DURING THE 3-WEEK STUDY TREATMENT PHASE:

- we may contact you by phone or e-mail about once a week to see how things are going; and
- ask you to record any change of medication that is made during the treatment phase.:

4 WEEK POST-PROCEDURE EVALUATION

The 4-week post procedure evaluation will take place 4 weeks after you have finished the 3-week treatment phase. During this time, you must continue to not do any other treatments to help with your foot pain including treatments with the Erchonia® EVRL™.

For the 4-week post-procedure evaluation, you must refrain from taking any pain medicine at least 6 hours prior to completing the evaluation form to:

- rate how painful your foot pain is to you at that time on a scale from 0 to 100, where '0' means 'no pain' and '100' means 'worst pain imaginable.'
- fill out a questionnaire about different symptoms of your foot pain
- rate how satisfied you are with the outcome of the treatment administration with the Erchonia® EVRL™ Laser on a five-point scale.

- record whether you believe you received treatments with the actual EVRL™ laser or the fake EVRL™ device and why you think this.

The 4-week post-treatment online evaluation takes about 15-20 minutes.

RISKS AND DISCOMFORTS
The complete risk profile or anticipated risks with the use of the Erchonia® EVRL™ 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 your foot pain or that they may even worsen.

Women 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
Your foot pain may lessen while you are in this study; however, this cannot be promised. The results of this study may help people to relieve foot pain associated with diabetic peripheral neuropathy 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® EVRL™ 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
If you finish the study, after the final 4-week post procedure, you will be paid $200 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 over-the-counter medicines like aspirin, ibuprofen, naproxen, acetaminophen, and capsaicin; topical creams such as lidocaine, salicylate and cortisone; prescription medications such as Celebrex, Lodine, and Relafen; antidepressants; anti-seizure drugs; opioid medicines, local anesthetic injections; surgical procedures; electrical nerve stimulation therapy; and hand or foot braces or orthopedic shoes. You do not have to be in this study to be treated for your foot pain.

COMPENSATION FOR INJURY
If you are injured or get sick from being in this study, call your doctor immediately. 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 sponsor.

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

What information may be used and given to others?

The study investigator 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 investigator 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 may be given to:

- The U.S. Food and Drug Administration (FDA),
- Department of Health and Human Services (DHHS) agencies,
- WCG IRB.

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 investigator. 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.

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.

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 otherwise entitled.

Your participation in this study may be stopped at any time by 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.

SOURCE OF FUNDING FOR THE STUDY

The sponsor, Erchonia Corporation, will pay for this research study.

QUESTIONS

Contact (PI Name) at (telephone number) (24 hours) 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 complaints about the research, you may contact:

WCG IRB

1019 39th Avenue SE Suite 120

Puyallup, Washington 98374-2115

Telephone: 855-818-2289

E-mail: researchquestions@wcgirb.com

WIRB is a group of people who independently review research.

WIRB will not be able to answer some study-specific questions, such as questions about appointment times. However, you may contact WIRB 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 Subject (18 years and older) Date

_____ _____

Signature of Person Conducting Informed Consent Discussion Date

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

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 may 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?

This permission will be good until December 31, 2060.

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 investigator. 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.

_____

Subject Name (printed)

CONSENT SIGNATURE:

_____ _____

Signature of Subject (18 years and older) Date

_____ _____

Signature of Person Conducting Informed Date

Consent Discussion