Erchonia® THL ™

A placebo-controlled, randomized, double-blind evaluation of the effect of the Erchonia® THL ™ for providing temporary relief from the symptoms of tinnitus

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Appendix B: Clinical Efficacy Testing

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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® THL™, manufactured by Erchonia Corporation (the Company), for prescription home use in providing relief of tinnitus symptoms when used by individuals in their own homes.

EXPECTED RESULTS
Following completion of the study procedure administration protocol with the Erchonia® THL ™, it is anticipated that compared with baseline, a significantly greater proportion of subjects in the test group than in the placebo group will show a 13-point or greater reduction in total score on the TFI at study endpoint evaluation relative to baseline.

STUDY DESIGN

This clinical study is a double blind, placebo-controlled, randomized design evaluation of the effect of the Erchonia® THL™ for prescription home use application in providing temporary relief from the symptoms of tinnitus.

This proposed clinical study design is based on the outcome of Pre-sub Q211668 agreed upon between Erchonia Corporation (Sponsor) and the FDA pertaining to a clinical study evaluating the effectiveness of the Erchonia 405 nm laser for the relief of the symptoms of tinnitus.

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 test procedure group or to the placebo procedure group of the clinical study, as follows:

Test procedure group: Subjects randomized to the test procedure group will self-administer the study procedures with the active (true) Erchonia® THL™ laser in his or her own home.

Control procedure group: Subjects randomized to the control procedure group will self-administer the study procedures with a 'fake' (placebo) Erchonia® THL™ 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 test and control 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 control devices.

Regardless of whether the subject self-administers the study procedures 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® THL™ device. Unblinding will occur after the final data set has been fully analyzed

The blinding procedure is as follows:

1) Each device is identified by an arbitrary number (serial number) and will be preassigned by the Sponsor to Group A which corresponds to the actual (test) THL™ devices or Group B which corresponds to the 'fake' devices. The serial number to device group translation will be maintained by the Sponsor until the final study data set analysis is complete
2) Each subject is randomly assigned to Procedure Group A or to Procedure Group B using the computer-generated randomization sequence stored and maintained confidentially at the Sponsor's work site.
3) Each subject will be assigned a device serial number by the Sponsor, which translates to Group A or Group B based on the subject's group randomization. The subject and the site personnel will not be aware of any grouping at all. The devices will only be identified by serial number.

4) The fake (placebo) Erchonia® THL™ is designed to have the same physical appearance as the actual Erchonia® THL™, including the appearance of any visible and invisible light output. Therefore, both the test and sham 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 procedure 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 procedure 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 'Procedure Group A' or to 'Procedure Group B' rather than to a test or placebo group, and only the Sponsor 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

Recruitment
Subjects will be recruited from the test site and online advertisements for individuals who have Tinnitus. Subject recruitment material found in Appendix O.

Compensation
A subject will receive financial compensation of $150 for his or her participation in this clinical study.

A subject will not be charged for the cost of use of the Erchonia® THL™ Laser or for the cost of any other evaluations or measurements that occur as part of his or her participation in the study.

Sample Size Determination

In the determination of sample size, the following parameters have been established for the purpose of assessing efficacy of the Erchonia® THL™ in this clinical study:

- Individual subject success criteria defined as a 13-point or greater reduction in total score on the Tinnitus Functional Index (TFI) from baseline to study endpoint evaluation.
- Overall study success criteria defined as a minimum 35% difference between the test device group and the placebo device group in the proportion of individual successes.
- It is anticipated that about 55% of subjects in the test 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.

In consideration of the above parameters established for the purposes of sample size calculation, the sample size of 29 subjects per procedure group (test 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.*

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 group.

Therefore, a minimum starting sample size of 32 subjects in each procedure group is needed to ensure sufficient numbers remain at the end of the trial (29 subjects per group) for any significant difference 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 procedure groups.

Justification for Sample Size Determination

The parameters selected for sample size determination are based on the industry-standard reference article: *Tinnitus handicap inventory for evaluating treatment effects: which changes are clinically relevant? Otolaryngol Head Neck Surg. 2011 Aug;145(2):282-7. Zeman F[1], Koller M, Figueiredo R, Aazevedo A, Rates M, Coelho C, Kleinjung T, de Ridder D, Langguth B, Landgrebe M.*

Additional details with respect to the reference values in this article are contained in the Statistical Analysis section below.

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. Tinnitus Variables

- Diagnosed etiology of tinnitus, if known. *Responses:* presbyacusis, noise-induced, unknown.
- Number of months/years since tinnitus onset.

B. Medication and Treatment

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

C. *Hearing Aid Use*: yes/no

D. ***Subject Demographics*****:** Subject age, gender, and ethnicity.

OUTCOME ASSESSMENT TOOLS

PRIMARY OUTCOME MEASURE ASSESSMENT TOOL:

Tinnitus Functional Index (TFI) (Appendix K)

The Tinnitus Functional Index (TFI) is commonly used in both clinical and research settings for tinnitus measurement due to its responsiveness to treatment-related change, validity for scaling the overall severity of tinnitus, and comprehensive coverage of multiple domains of tinnitus severity (Meikle et al., 2011). The self-report questionnaire, consists of 25 items with a response option on an 11-point Likert scale from 0–10

The calculation of overall TFI score is as follows:
(1) Sum all valid answers (maximum possible score = 250 if the respondent were to rate all 25 TFI items at the maximum value of 10).
(2) Divide (1) by the number of questions for which the sum of the valid answers was based to yield the respondent's mean item score.
(3) Multiply (2) by 10 to attain the respondent's overall TFI score (0-100 range).

Total TFI score can be categorized as Level of Tinnitus Severity as follows:

TFI 0 to 17: Not a problem
TFI 18 to 31: Small problem
TFI 32 to 53: Moderate problem
TFI 54 to 72: Big Problem
TFI 73 to 100: Very big problem

DIAGNOSTIC, SECONDARY, and SAFETY OUTCOME ASSESSMENT TOOLS

Audiometric Testing: Degree of Hearing Loss

Audiometric testing will be performed as follows:

- Pure tone air conduction testing for the frequencies of 250 Hz, 500 Hz, 1 kHz, 2 kHz, 4 kHz, 8kHz, 12 kHz, 16 kHz, and 20 kHz
- Pure tone bone conduction testing for the frequencies of 250 Hz, 500 Hz, 1 kHz, 2 kHz, 4 kHz, and 8kHz.

Audiometric testing will be performed using standardized, calibrated equipment that is held constant across all subjects at the test site and administered according to standard industry procedures and protocols.

The audiogram results will be used for two purposes in this study:

(i) Calculation of pure tone average (PTA) as a part of Study Qualification evaluation.

Pure Tone Average (PTA) is calculated as follows: PTA = (500 Hz dB + 1 kHz dB + 2 kHz dB) / 3.

(ii) For tracking of changes in PTA and hearing levels across study duration from 250 Hz through 20 kHz for efficacy and safety evaluation.

Tympanometry

Tympanometry is an objective test of middle-ear function. It is an acoustic evaluation of the condition of the middle ear eardrum (tympanic membrane) and the conduction bones by creating variations of air pressure in the ear canal. Tympanometry, together with audiometry, assists in distinguishing between sensorineural and conductive hearing loss,

The test is performed by inserting the tympanometer probe in the ear canal. The instrument changes the pressure in the ear, generates a pure tone, and measures the eardrum responses to the sound at different pressures. This produces a series of data measuring how admittance varies with pressure, which is plotted as a tympanogram:

Tympanograms are categorized according to the shape of the plot. A normal tympanogram shows normal pressure in the middle ear with normal mobility of the eardrum and ossicles and is labelled Type A. Type B tympanograms indicate (a) fluid in the middle ear, (b) perforation of the tympanic membrane or patent pressure equalization tube, or (c) a tumor in the middle ear. Type C tympanograms are consistent with negative pressure in the middle ear space resulting from compromised eustachian tube function and a retracted tympanic membrane.

A Type A tympanogram accompanied by hearing loss where the air conduction and bone conduction levels on an audiogram are comparable is consistent with a sensorineural hearing loss.

A Type B or Type C tympanogram accompanied by hearing loss where there is a gap / difference between the air conduction and bone conduction thresholds on the audiogram at all or some frequencies is consistent with a conductive or mixed hearing loss.

Otoscopic Exam of the Ears

Otoscopy is a clinical procedure used to examine the structures of the ear, particularly the external auditory canal, tympanic membrane, and middle ear. Otoscopy is performed using a standard otoscope, a tool that shines a beam of light to help visualize and examine the condition of the ear canal and eardrum. The otoscopic exam is performed by gently pulling the auricle upward and backward to move the acoustic meatus in line with the canal.

The appearance of a normal healthy middle ear is as follows:

- Auditory canal: Some hair, often with yellow to brown cerumen.

- Ear drum:
  - Pinkish gray in color; shiny, translucent and in neutral position.
  - Intact; no bulging or retraction.
  - Malleus lies in oblique position behind the upper part of drum.

Observations from the otoscopic examination of the ear will be recorded, taking into consideration the following factors and any other of consideration:

- External auditory canal:
  - Hair (none, some, excessive)
  - Cerumen:
    - color (yellow, brown)
    - amount: minimal, normal (≤ 50%); impacted (> 50%)
    - foreign body (yes/no)
  - Discharge or drainage (yes/no)

- Tympanic membrane
  - Color (pinkish-grey, red, white, yellow)
  - Translucency (transparent, opaque)
  - Position of the drum (retracted, neutral, or bulging)
  - Perforation / scars (yes/no)
  - Cone of light observed (yes/no)

- Position of the malleus handle: normal (behind the upper part of the drum); other

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 tinnitus following completion of the laser administration procedures with the Erchonia® THL™ 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 tinnitus 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 procedures with the true or fake Erchonia® THL™ and records verbatim his or her reasoning or rationale for this perceived determination.

STUDY PROCEDURE PROTOCOL

STUDY QUALIFICATION

SIGNING OF INFORMED CONSENT FORM

The site investigator will commence by presenting and reviewing the items in the informed consent form with the potential participant and answer any questions he or she may have. To proceed, the individual must willingly sign the informed consent form.

ASSIGNMENT OF SUBJECT IDENTIFICATION NUMBER

The subject is assigned a unique subject identification number based upon his or her order of entry into the study.

Additional information about the informed consent and subject ID number assignment is contained in a later section of the protocol titled, “SAFETY AND CONFIDENTIALITY ISSUES.”

SUBJECT RANDOMIZATION TO PROCEDURE GROUP

Following signing of the consent form and prior to study qualification evaluation, a subject is randomly assigned to Procedure Group A or to Procedure Group B, following the methodology outlined above in the STUDY DESIGN section of the protocol.

STUDY QUALIFICATION EVALUATION

A suitably qualified and licensed health professional (study investigator) will perform the study qualification evaluation, at the test site. To be eligible for study participation a subject must satisfy the following qualification criteria.

The study inclusion and exclusion criteria have been separated into two parts: Part 1 and Part 2. This is done to avoid lengthy study tool evaluations (TFI & Audiometric Test) that are involved in Inclusion and Exclusion Part 2, if the subject does not first meet all the Inclusion Part 1 and / or Exclusion Part 1 criteria.

INCLUSION CRITERIA PART 1

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

- Bilateral tinnitus
- Current diagnosis of subjective tinnitus
- 18 years of age or older
- Able to read and write English
- Constant tinnitus on-going over at least the past 6 months
- Willing to abstain from other tinnitus-related treatments, except existing hearing aid use, throughout the study duration.

EXCLUSION CRITERIA PART 1

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

- Tympanosclerosis
- Meniere's disease
- Acoustic neuroma(s)
- Current and consistent use of ototoxic medication(s)
- Presbycusis
- Thyroid disease
- Skull fracture
- Traumatic brain injury (TBI)
- Significant depression or other significant mental health condition that in the opinion of the study investigator may interfere with the individual's ability to participate in the study.
- Syphilis
- Retrocochlear tumor(s)
- Pregnant, possibly pregnant, or breastfeeding.
- Open wounds (sores, cuts, ulcers, etc.) on or around the ears or neck
- Cancerous growths or being treated for cancerous growths on or around the ears or neck
- Previous experience self-administering laser therapy
- 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.

INCLUSION CRITERIA PART 2

A subject that satisfies both the Inclusion Part 1 and Exclusion requirements will proceed to Inclusion Criteria Part 2:

- Tinnitus Functional Index (TFI) total score of 32 to 72, inclusive (Level 3 or 4)

Conduct of the following evaluations:

- Audiometric Testing: calculation of PTA for each ear
- Tympanometry
- Otoscopic Examination of the Ears
-

Based on the outcome of the above evaluations:

- Pure Tone Audiometry (PTA) is ≤ 60 dB (Moderate or less) for each of the right and left ears
- No hearing loss or sensorineural hearing loss only, bilaterally.

EXCLUSION CRITERIA PART 2

- Impacted cerumen, foreign bodies, or tubes in one or both ears
- Perforation of the eardrum in one or both ears
- Discharge and/or drainage from one or both ears

PRE-PROCEDURE EVALUATION PHASE

The pre-procedure evaluation phase commences the same day following successful study qualification. The pre-procedure evaluation will be performed at the test site and the following will be recorded by the site investigator as outlined in the STUDY TEST BATTERY section above.

BASELINE VARIABLES

- Tinnitus Variables
- Existing hearing aid use
- Medication and Treatment
- Subject Demographics

PRE-PROCEDURE OUTCOME ASSESSMENTS

The Pre-Procedure outcome measures can be taken from the "Study Qualification Evaluation" measures if each are performed on the same day.

- Tinnitus Functional Index (TFI)
- Audiometric Test: calculation of PTA for each ear
- Tympanometry
- Otoscopic Examination of the Ears

AT-HOME PROCEDURE ADMINISTRATION PHASE

A fully-qualified enrolled subject will be provided by the study site, a device serial number, which translates to Group A or Group B based on the subject's group randomization. The subject and the site personnel will not be aware of any grouping at all. The devices will only be identified by serial number (see Randomization). The device will include a THL™ Proper Use Reference Guide **(Appendix D).**

PROCEDURE ADMINISTRATION

- The procedure administration phase extends over 4 consecutive weeks.
- The subject self-administers one procedure administration with the Erchonia® THL ™ (A or B) on each consecutive day of the 4-week procedure administration phase for a total of 28 self-administered procedures.
- Each procedure administration lasts 5 minutes each ear, for a total treatment time of 10 minutes.
- Each procedure is self-administered by the subject in his or her own home.

PROCEDURE ADMINISTRATION PROTOCOL

The subject will need to follow the instructions in the Erchonia THL ™ Proper Use Reference Guide to correctly self-administer a procedure. These instructions read as follows:

1. Turn the THL ™ device on by pressing and holding the "Power Switch" for 3 seconds.

2. Ensure the green POWER ON indicator light is lit.

3. Put on the laser safety goggles provided.

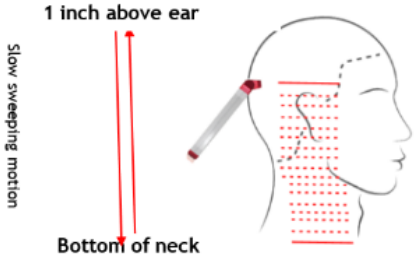
4. Once the safety goggles are on, start the laser treatment by pressing the “START” icon on the treatment screen. Note: The protocol software is factory set and cannot be changed.

5. Ensure the laser indicator light is lit.

6. Hold the THL ™ laser light diode about 1 inch above your right ear and about 4 inches from your skin.

7. In a slow continuous sweeping motion, move the THL ™ down the right side of your neck.

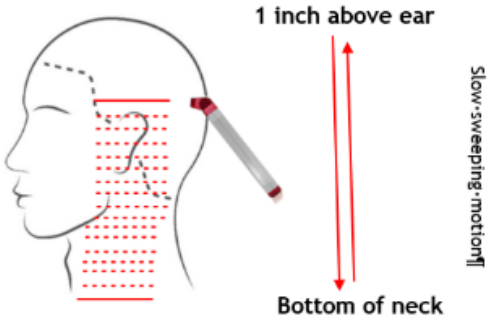
8. Once you reach the bottom of your neck, in a slow continuous sweeping motion. move the THL ™ up your neck back to where you started, about 1 inch above your right ear, making sure to keep the laser about 4 inches away from the surface of your skin the whole time. This process is shown in the diagram below.



9. Continue this up and down sweeping motion on the right side for the whole 5 minutes of treatment.

10. Once the 5 minutes is done, the treatment will automatically stop. The “Time Remaining” display shows 0:00 and the laser lights and the laser indicator light will turn off.

11. Next, repeat steps 4 through10 for your left side (left ear and left side of neck) as shown in the diagram below.



12. After you have treated both your right and left ears for a total treatment time of 10 minutes, the treatment session is complete, and you may remove the safety googles.

PROCEDURE ADMINISTRATION PHASE MEASURES

DAILY TREATMENT ADMINISTRATION LOG

The study site will provide the subject data capture forms to record each day when they have administered a treatment with the Erchonia® THL ™ Laser. The subject will provide the study investigator the completed "Treatment administration log" following the 4-week treatment procedure administration phase.

WEEKLY ASSESSMENTS

Once a week, the site staff may call and/or contact the subject by e-mail to check on compliance, to verify that no adverse events had occurred, and to answer any questions the subject may have.

4 WEEK EVALUATION: TREATMENT END

Following completion of the entire 4 weeks of study procedure administrations with the Erchonia® THL ™, the following will be recorded by the site investigator as outlined in the STUDY TEST BATTERY section above.

- Tinnitus Functional Index (TFI)
- Audiometric Test: Degree of Hearing Loss
- Tympanometry
- Otoscopic Examination of the Ears
- Subject Satisfaction With Study Outcome
- Subject Perceived Group Allocation and Rationale

POST-PROCEDURE ACTIVITIES

2 Weeks Post-Procedure: STUDY ENDPOINT

Two weeks following the completion of the 4-week treatment administration phase, the following will be recorded by the site investigator) 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.

- Tinnitus Functional Index (TFI)
- Audiometric Test: Degree of Hearing Loss
- Tympanometry
- Otoscopic Examination of the Ears
- Subject Satisfaction With Study Outcome
- Subject Perceived Group Allocation and Rationale

ADVERSE EVENTS

The subject will be instructed to notify the PI any time that a potential adverse event has been experienced. 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® THL™ 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 stored in that subject's file at all times other than when information is being recorded on them.

Copies of all of the subject case report forms will be made and supplied to Regulatory Insight, Inc. and Erchonia Corporation. Regulatory Insight, Inc. and Erchonia Corporation will maintain these copies in a separate clinical study file that is kept in a locked filing cabinet at 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

BASELINE VARIABLES EVALUATION

A. Tinnitus Variables

Baseline tinnitus variables of tinnitus etiology, and time since tinnitus onset will be summarized descriptively (mean and standard deviation, and categorically, as applicable) and compared for differences between procedure groups and test sites, as applicable. Any identified differences will be explored with respect to impact on study outcome.

B. Medication and Treatment

Subjects' prior treatment approaches for tinnitus reduction and baseline concomitant medication and therapy use will be summarized categorically and compared for differences between

procedure groups and test sites. Any identified differences will be explored with respect to impact on study outcome.

C. Hearing Aid Use

Subjects' use of hearing aids will be summarized descriptively. Any identified differences will be explored with respect to impact on study outcome.

***D. Subject Demographics*:**

Demographics of age, gender and ethnicity will be summarized descriptively (mean and standard deviation, and categorically, as applicable) and compared for differences between procedure groups and test sites. Any identified differences will be explored with respect to impact on study outcome.

PRIMARY EFFICACY OUTCOME MEASURE: CHANGE IN TOTAL SCORE ON THE TINNITUS FUNCTIONAL INDEX(TFI) FROM BASELINE TO STUDY ENDPOINT

Primary efficacy outcome measure for this clinical study is a statistically significant difference in the proportion of subjects between test and control groups who achieve a clinically meaningful decrease in total score on the TFI from baseline to study endpoint.

The TFI has been highly recommended to be used in both clinical and research settings for tinnitus measurement because of its responsiveness to treatment-related change, validity for scaling the overall severity of tinnitus, and comprehensive coverage of multiple domains of tinnitus severity (Meikle et al., 2011).

The following abstract pertains to a reference study that served to establish the industry-standard minimal clinically relevant difference of change in TFI total score from pre- to post-intervention as 13 points. This reference has been cited and supported through numerous subsequent prospective and retrospective trials and analyses and is considered industry-wide.

Meikle MB, Henry JA, Griest SE, Stewart BJ, Abrams HB, McArdle R, Myers PJ, Newman CW, Sandridge S, Turk DC, Folmer RL, Frederick EJ, House JW, Jacobson GP, Kinney SE, Martin WH, Nagler SM, Reich GE, Searchfield G, Sweetow R, Vernon JA. The tinnitus functional index: development of a new clinical measure for chronic, intrusive tinnitus. Ear Hear. 2012 Mar-Apr;33(2):153-76.

Objectives: Chronic subjective tinnitus is a prevalent condition that causes significant distress to millions of Americans. Effective tinnitus treatments are urgently needed but evaluating them is hampered by the lack of standardized measures that are validated for both intake assessment and evaluation of treatment outcomes. This work was designed to develop a new self-report questionnaire, the Tinnitus Functional Index (TFI), that would have documented validity both for scaling the severity and negative impact of tinnitus for use in intake assessment and for measuring treatment-related changes in tinnitus (responsiveness) and that would provide comprehensive coverage of multiple tinnitus severity domains.

Design: To use preexisting knowledge concerning tinnitus-related problems, an Item Selection Panel (17 expert judges) surveyed the content (175 items) of nine widely used tinnitus questionnaires. From those items, the Panel identified 13 separate domains of tinnitus distress

and selected 70 items most likely to be responsive to treatment effects. Eliminating redundant items while retaining good content validity and adding new items to achieve the recommended minimum of 3 to 4 items per domain yielded 43 items, which were then used for constructing TFI Prototype 1.Prototype 1 was tested at five clinics. The 326 participants included consecutive patients receiving tinnitus treatment who provided informed consent-constituting a convenience sample. Construct validity of Prototype 1 as an outcome measure was evaluated by measuring responsiveness of the overall scale and its individual items at 3 and 6 mo follow-up with 65 and 42 participants, respectively. Using a predetermined list of criteria, the 30 best-functioning items were selected for constructing TFI Prototype 2.Prototype 2 was tested at four clinics with 347 participants, including 155 and 86 who provided 3 and 6 mo follow-up data, respectively. Analyses were the same as for Prototype 1. Results were used to select the 25 best-functioning items for the final TFI.

Results: Both prototypes and the final TFI displayed strong measurement properties, with few missing data, high validity for scaling of tinnitus severity, and good reliability. All TFI versions exhibited the same eight factors characterizing tinnitus severity and negative impact. Responsiveness, evaluated by computing effect sizes for responses at follow-up, was satisfactory in all TFI versions. In the final TFI, Cronbach's alpha was 0.97 and test-retest reliability 0.78. Convergent validity (r = 0.86 with Tinnitus Handicap Inventory [THI]; r = 0.75 with Visual Analog Scale [VAS]) and discriminant validity (r = 0.56 with Beck Depression Inventory-Primary Care [BDI-PC]) were good. The final TFI was successful at detecting improvement from the initial clinic visit to 3 mo with moderate to large effect sizes and from initial to 6 mo with large effect sizes. Effect sizes for the TFI were generally larger than those obtained for the VAS and THI. **After careful evaluation, a 13-point reduction was considered a preliminary criterion for meaningful reduction in TFI outcome scores.**

Conclusions: The TFI should be useful in both clinical and research settings because of its responsiveness to treatment-related change, validity for scaling the overall severity of tinnitus, and comprehensive coverage of multiple domains of tinnitus severity.

The complete article is contained in Appendix L.

Based on this established reference, the following criteria are established to determine efficacy of self-application of the Erchonia® THL™ to relieving the symptoms of tinnitus in adults.

<u>Subjects Meeting Individual Success Criteria</u>
Individual subject success criteria is defined as a 13-point or greater decrease in total TFI score at study endpoint relative to baseline.

<u>Overall Study Success Criteria.</u>
Overall study success criteria is defined as at least a 35% difference between procedure groups, comparing the proportion of individual successes in each group. It is anticipated that about 55% of subjects in the test group will meet the individual success criteria and about 20% of subjects in the control group will meet the individual success criteria.

Each of the three following studies utilized the Tinnitus Functional Index (TFI) as the primary efficacy outcome with the minimal clinically relevant difference of change in TFI total score from pre- to post-intervention defined as 13 points as per the reference article cited above by Meikle, MB, et al. (2012).

The table below presents the number and percentage of individual subjects who attained or exceeded the MCID of a 13-point change in TFI total score pre- to post-treatment for each of the three randomized controlled trials (RCTs) for subjects in each of the active and sham/placebo groups. The differences in these proportions between treatment groups ranged from 25% to 34%, with the differences of 30% and 34% each determined to be statistically significant at $p<0.05$ and $p<0.005$, respectively. These RCTS therefore support the overall success criteria of a 35% difference between treatment groups implemented in the current study as being both statistically significant and clinically meaningful and highly conservative. The individual group anticipated proportions of 20% and 55% for placebo and active treatment groups, respectively is further supported by the outcome of the Folmer, RL et al. (2015) study listed below.

Study	Active Group: n attaining individual MCID/Total n	Placebo Group: n attaining individual MCID/Total n	Difference between groups	p-value
Robert L. Folmer, PhD; Sarah M. Theodoroff, PhD; Linda Casiana, MS, CCRP et al; Yongbing Shi, MD, PhD; Susan Griest, MPH; Jay Vachhani, AuD Repetitive Transcranial Magnetic Stimulation Treatment for Chronic Tinnitus: A Randomized Clinical Trial JAMA Otolaryngol Head Neck *Surg.* 2015;141(8):716-722.	18/32 = 56%;	7/32 = 22%;	34%	<0.005
Maxwell, Kenneth S.*; Robinson, James M.; Hoffmann, Ines; Hou, Huiying J.; Searchfield, Grant; Baguley, David M.; McMurry, Gordon; Piu, Fabrice†; Anderson, Jeffery J. Intratympanic Administration of OTO-313 Reduces Tinnitus in Patients With Moderate to Severe, Persistent Tinnitus: A Phase 1/2 Study Otology & Neurotology: December 2021 - Volume 42 - Issue 10	6/14 = 43%;	2/16 = 13%;	31%	<0.05
Theodoroff, S.M., Griest, S.E. & Folmer, R.L. Transcranial magnetic stimulation for tinnitus: using the Tinnitus Functional Index to predict benefit in a randomized controlled trial. Trials 18, 64 (2017).	18/25 = 51%	9/35 = 26%	25%	Not reported

Hypotheses

- ***Null Hypothesis***: There will be no statistically significant difference in the proportion of individual successes, as defined, between the test and control groups.
- ***Alternative Hypothesis***: There will be a statistically significant difference in the proportion of individual successes, as defined, between the test and control groups, to the effect of 35% or greater.

PRIMARY EFFICACY OUTCOME STATISTICAL EVALUATION METHODS

- **Intent to Treat (ITT) Principle**: Primary efficacy analysis will be according to the intent to treat (ITT) principle; wherein subjects will be included in the analysis if they were randomized to study procedure group and had a valid baseline (pre-procedure) visit including recording of the TFI.

- **Missing data** will be handled through multiple imputation analysis is a strategy to handle missing values in a clinical trial wherein each missing value is replaced with a set of plausible values that represent the uncertainty about the right value to impute. Multiple imputation does not attempt to estimate each missing value through simulated values, but rather to represent a random sample of the missing values. This process results in valid statistical inferences that properly reflect the uncertainty that results from missing values, such as valid confidence intervals for parameters.

  Multiple imputation inference involves three distinct phases:

  1. The missing data are filled in m times to generate m complete data sets.
  2. The m complete data sets are analyzed by using standard statistical procedures.
  3. The results from the m complete data sets are combined for the inference.

  Multiple imputation usually assumes that the data are missing at random (MAR). That is, for a variable Y, the probability that an observation is missing depends only on the observed values of other variables, not on the unobserved values of Y.

- **Per-Protocol Analysis** will also be performed for the set of all subjects who were randomized to procedure group and completed the study according to the full protocol.

- **Primary analysis of efficacy** will be according to intent to treat (ITT) analysis through the application of:

  1) **Fisher's exact test** to compare the proportion of individual successes between the test and the control groups, considering that randomization has been diligently conducted and important covariates between the two groups are well balanced.

  2) **Parametric ANCOVA model** analysis with the mean change from baseline to study endpoint in TFI score as the dependent variable, procedure group as the independent variable of interest and baseline TFI score as a covariate. A two-tailed significance level of 5% will be considered statistically significant.

- **Covariates:** The following potential covariate baseline variables will be adjusted, as applicable, through application of an ANCOVA analysis for the continuous variables and linear regression analysis for categorical variables.

  - ✓ Baseline Audiometric Test: PTA
  - ✓ Age, gender, ethnicity
  - ✓ Tinnitus etiology and duration
  - ✓ Use/non-use of hearing aids

ADDITIONAL SUPPORTIVE EVALUATIONS

The following exploratory qualitative trending within and between procedure groups will be conducted descriptively across all applicable assessments at baseline, treatment endpoint (4 weeks), and 2 weeks post-procedure evaluations, without claims of statistical significance:

a. mean changes in total TFI scores and categories across and between procedure groups across all three evaluations of pre-treatment, treatment end, study endpoint, and post-treatment.
b. changes in audiometric evaluations, including PTAs.

COMPLIANCE EVALUATION

Subject's self-reported compliance with treatment administration will be evaluated. Deviations in compliance will be reported and evaluated with respect to impact on study outcome evaluation.

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 procedure administration phase (study endpoint).

Statistical evaluation of blinding efficacy will be performed as follows:

(i) The percentage of subjects who correctly perceived their procedure group assignment and the percentage of subjects who did not correctly perceive their procedure group assignment will be calculated.
(ii) The **Fischer's Exact categorical analysis technique** for comparison of proportion of successes (accurate procedure group assignment determination) and failures (inaccurate procedure group assignment determination) between subject groups will be performed for each of the subject.
(iii) **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.: 'I barely notice my tinnitus anymore, so I believe I got the real treatment' or 'I haven't noticed any change in my tinnitus, 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, such as 'I saw/didn't see a light go on'.

SAFETY ANALYSES

Safety analyses will be based on all subjects who were randomized to the test or to the placebo procedure group. Safety will be assessed by evaluating and comparing frequency and incidence of observed and/or reported adverse events between test and placebo procedure 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 group subjects.

Additionally, safety will be assessed through tracking of the following across study duration:

a. changes in audiometric evaluations, including PTAs.
b. Changes in tympanogram type.
c. Changes in otoscopic evaluation findings.

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 M.**

CASE REPORT FORMS

The case report forms that will be used to collect the data from each subject in this clinical study can be found in **Appendix N**.

END OF DOCUMENT