STUDY DOCUMENT COVER PAGE

Official Title:

Clinical Efficacy and Long-Term Durability of a Steady-State Coherent Biomodulator Patch in Subjective Tinnitus: A Randomized, Double-Blind, Placebo-Controlled Study

NCT Number: [To be assigned upon registration]

Document Type: Study Protocol with Statistical Analysis Plan and Informed Consent Form

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Approving Ethics Committee: Istanbul Medeniyet University Goztepe Training and Research Hospital Clinical Research Ethics Committee (2013-KAEK-64)

Approval Number: 2018/0174

PART 1: STUDY PROTOCOL

1. Background and Rationale

Tinnitus is a common condition without a universally accepted pharmacological treatment. The steady-state coherent biomodulator patch (Antinitus, Sensori AB, Sweden) uses passive, light photon-driven technology intended to influence water coherency in tissue and modulate neural activity along auditory pathways. Tinnitus is regarded as a symptom rather than a disease in itself; accordingly, the biomodulator patch used in this study is not intended to cure or eliminate tinnitus, but to reduce the associated distress. This technology was developed in Sweden and has been studied across various applications since 1990. A prior pilot study found no safety concerns associated with its use for tinnitus.

2. Study Objectives

Primary Objective

To evaluate the effect of the biomodulator skin patch on tinnitus, specifically the change in Tinnitus Handicap Inventory (THI) score from baseline to Day 51.

Secondary Objectives

To evaluate changes in THI at Day 21 and at 1-year follow-up, and changes in Hyperacusis Questionnaire (HQ) and Hospital Anxiety and Depression Scale (HADS) scores across follow-up assessments.

3. Study Design

This is a single-center, randomized, double-blind, placebo-controlled, parallel-group clinical trial. Participants were randomized in a 1:1 ratio to an experimental group (active biomodulator patch) or a control group (placebo patch), in order to evaluate the therapeutic effect of the active patch against the placebo effect. The trial did not involve testing of a new surgical method, stem cell transplantation, tissue transplantation, or organ transplantation.

4. Study Population

Inclusion Criteria

- Age older than 18 years
- Subjective tinnitus for at least 4 weeks
- Visual Analog Scale (VAS) score of at least 3 (on a 0–10 scale)
- Willingness to provide informed consent
- Completed otolaryngologic examination with no serious underlying health condition

Exclusion Criteria

- Presence of dermatological conditions (risk of skin irritation from patch application)
- Initiation of any tinnitus treatment within 6 weeks prior to study entry

- Current participation in another experimental study
- Prior use of the biomodulator skin patch

5. Sample Size

The study was designed to enroll 40 participants in the experimental group and 40 participants in the control group (80 total). A total of 91 participants were ultimately enrolled to account for anticipated attrition; 80 participants completed the study (40 per group). There were no withdrawals due to adverse effects. The 11 participants who did not complete the study primarily missed follow-up visits due to travel, holidays, or personal reasons; one participant withdrew after reporting spontaneous resolution of tinnitus.

6. **Interventions**

Participants in the experimental group applied an active biomodulator patch behind the ear, replaced daily, for three weeks. Participants in the control group applied a placebo patch, visually indistinguishable from the active patch, under the same schedule. Active and placebo patches were sealed in identical envelopes by a third party who recorded the allocation key separately; this key was not accessed by the investigator until the study concluded. All participants additionally received a standardized one-hour informative counseling session at study entry, covering the auditory system, the nature and causes of tinnitus, and available management strategies.

7. Randomization and Blinding

Participants were randomly assigned in a 1:1 ratio to the experimental or control group. The study was double-blind: participants, the investigator (who also served as care provider and outcomes assessor), were all unaware of group allocation for the duration of the study. Allocation concealment was maintained through sealed, visually identical envelopes prepared by an independent third party.

8. Outcome Assessments and Study Procedures

Assessments were performed using validated questionnaires only (no laboratory testing or invasive procedures): the Tinnitus Handicap Inventory (THI), the Hyperacusis Questionnaire (HQ), the Hospital Anxiety and Depression Scale (HADS), and Visual Analog Scale (VAS) ratings of tinnitus-related distress. Assessments were conducted at baseline, after 21 days of patch use, at Day 51 (approximately one month after treatment completion), and via telephone follow-up at approximately one year post-treatment for a subset of participants.

9. Study Duration

The planned enrollment period was approximately 12 months, with a maximum treatment duration of 3 weeks per participant and follow-up extending to approximately 1 year.

10. Data Monitoring

No independent data monitoring committee was appointed for this study, consistent with its single-center, non-invasive, minimal-risk design.

11. Ethical Considerations

This study was reviewed and approved by the Istanbul Medeniyet University Goztepe Training and Research Hospital Clinical Research Ethics Committee (2013-KAEK-64), Approval No. 2018/0174, dated May 17, 2018. All participants provided written informed consent prior to enrollment. The study was conducted in accordance with the Declaration of Helsinki and applicable national regulations for non-drug clinical research.

PART 2: STATISTICAL ANALYSIS PLAN

1. General Approach

Continuous variables were assessed for normality. Given that several continuous variables were not normally distributed, continuous data are summarized as median and interquartile range (IQR); categorical data are presented as counts and percentages.

2. Between-Group Comparisons

Between-group comparisons of continuous variables at baseline and follow-up were conducted using the Mann–Whitney U test. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. All analyses used available data for each variable and time point (i.e., no imputation of missing data).

3. Within-Group Longitudinal Analysis

For THI and HQ, pairwise within-group comparisons across PRE, POST21, POST51, and POST_1Y were conducted using Wilcoxon signed-rank tests, with overall time effects evaluated using Friedman tests on complete cases across all four time points. For HADS anxiety, HADS depression, and HADS total score, Wilcoxon signed-rank tests and Friedman tests were applied across the three available time points (PRE, POST21, POST51). Kendall's W was reported as the effect-size measure for Friedman tests; Wilcoxon effect sizes were expressed as r.

4. Secondary and Exploratory Analyses

Additional between-group analyses were performed on raw post-treatment scores at POST21 and POST51, and on change from baseline to 1 year for THI and HQ. As exploratory analyses, cross-sectional associations among tinnitus handicap, emotional distress, hyperacusis burden, age, and tinnitus duration were examined using Spearman rank correlations at baseline, POST21, and POST51. Group-specific linear regression models were constructed at POST21 and POST51, with THI as the dependent variable and HADS anxiety, HADS depression, HQ, and tinnitus duration entered simultaneously as predictors. HADS total score was excluded from regression models due to collinearity with its anxiety and depression subscales.

5. Significance Threshold

Two-sided p values less than 0.05 were considered statistically significant throughout.

PART 3: INFORMED CONSENT FORM

Clinical Study: "Investigation of the Effect of a Biomodulator Skin Patch on Tinnitus"

Dear Participant,

This study aims to investigate the effectiveness of a biomodulator skin patch applied to patients who have symptoms of tinnitus (ringing in the ears). In this study, a biomodulator patch or a patch without biomodulator activity will be randomly placed behind your ear; no other procedure will be performed, and you will not be harmed in any way. If you agree to take part in the study, you will be asked to complete questionnaires about your tinnitus before the intervention begins. You will be given 21 skin patches, which must be changed daily, and asked to apply a new patch to the area behind your ear every day for 21 days. At the end of the 21 days, and again at the end of the 7th week, you will be asked to complete the same questionnaires about your tinnitus.

Participation in this study is voluntary. You have the right to refuse to participate or to withdraw from the study at any stage. This will not result in any negative consequences or obstacles to your future treatment.

If you take part in this study, the results obtained will be published for scientific purposes only, without disclosing your identity. No fee will be requested from you for this study. You are completely free regarding participation in the study. Whether or not you participate will not lead to any change in the medical care and attention shown to you.

This study is being carried out with the permission of our hospital's ethics committee. Our study is supervised by Prof. Dr. M. Tayyar Kalcioglu and conducted by Murat Erinc, Audiologist. If you need to reach Murat Erinc for any reason, you may contact him by email at murat.erinc@medeniyet.edu.tr or by phone at 0216 566 6600, extension 4311.

Thank you for your participation.

Murat Erinc, Audiologist

Date:

Signature:

I voluntarily agree to participate in this study. I have read the informed consent text above. Verbal explanations regarding this information were provided to me. I understand that I may withdraw from the study at any time, with or without giving a reason. Under these conditions, I agree to participate in this study of my own free will, without any pressure or coercion.

Regarding the results of the study "Investigation of the Effect of a Biomodulator Skin Patch on Tinnitus," I permit:

☐ Use only in the above-mentioned study

☐ Use in all future planned studies

☐ Do not permit use under any circumstances

Participant's Name and Surname:

Phone and Address:

Signature:

Date of Birth: Date:

Investigator's Name: Signature:

If the participant is unable to understand:

Name, Surname, and Relationship of Participant's Legal Representative:
Signature:

Witness Name and Surname: Signature: