

**Title of Clinical Study:**

Treatment Evaluation of Neuromodulation for Tinnitus - Stage A2 (TENT-A2)

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**Protocol Paper Title:**

Non-invasive bimodal neuromodulation for the treatment of tinnitus: a study protocol for a second large-scale double-blind randomised clinical trial to confirm and further optimise stimulation parameters

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**Running Title:** Bimodal neuromodulation for the treatment of tinnitus

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## **ABSTRACT**

**Introduction:** There is increasing evidence from animal and human studies that bimodal neuromodulation combining sound and electrical somatosensory stimulation can induce extensive brain changes and treat tinnitus. The main objectives of the proposed clinical study are to: (1) confirm the efficacy, safety and patient tolerability demonstrated in a previous large-scale study of bimodal auditory and trigeminal nerve stimulation (TENT-A1); (2) evaluate the therapeutic effects of adjusting stimulation parameters over time, and (3) determine the contribution of different features of bimodal stimulation in improving tinnitus outcomes.

**Methods and analysis:** This study will be a prospective, randomised, double-blind, parallel-arm, comparative clinical trial of a 12-week treatment for tinnitus using a CE-marked device with a pre-post and 12-month follow-up design. Four treatment regimens will be investigated, in which each regimen consists of two different stimulation settings with the first setting presented during the first 6 weeks and the second setting presented during the second 6 weeks of treatment. The study will enrol 192 patients, split 80:80:16:16 across the four arms. Patients will be randomised to one of four arms and stratified to minimise baseline variability in four categories: two separate stratum for sound level tolerance (using loudness discomfort level as indicators for hyperacusis severity), high tinnitus symptom severity based on the Tinnitus Handicap Inventory (THI) and tinnitus laterality. The primary efficacy endpoints are within-arm changes in THI and Tinnitus Functional Index (TFI) as well as between-arm changes in THI after 6 weeks of treatment. Additional efficacy endpoints include within-arm or between-arm changes in THI after 6 or 12 weeks of treatment and in different subtypes of patients, as well as at post-treatment assessments at 6 weeks, 6 months and 12 months. Treatment safety, attrition rates and compliance rates will also be assessed and reported.

**Ethics and dissemination:** This study protocol is approved by the Tallaght Hospital / St. James's Hospital Joint Research Ethics Committee in Dublin, Ireland. Findings will be disseminated to relevant research, clinical, health service and patient communities through publications in peer-reviewed journals and presentations at scientific and clinical conferences.

**Trial registration number:** The trial is registered on ClinicalTrials.gov (NCT03530306). The Sponsor is Neuromod Devices Limited in Dublin, Ireland.

## **STRENGTHS AND LIMITATIONS OF THIS STUDY**

- The main strength of this study is that it is a large, double-blind, randomised clinical trial that will provide confirmatory evidence of the safety, efficacy and patient tolerability demonstrated in a previous large, double-blind, randomised clinical trial.
- Building on the previous trial, this study will further inform our understanding of the contribution or necessity of different sound and tongue stimulation parameters on the clinical efficacy of bimodal stimulation for tinnitus treatment.
- This study will comprehensively assess the therapeutic effect of different stimulation parameters in predefined patient subtypes that will refine candidature and improve personalization for the intervention in tinnitus patients, in which there are very few large-scale treatment studies providing such subtyping data in the tinnitus field.
- A limitation of the study design is that the efficacy due to stimulation settings used during the second 6 weeks of treatment may not be directly comparable with efficacy due to the stimulation settings in the first 6 weeks of treatment because of possible carry-over effects. Instead, the cumulative effects from both stimulation settings used in each treatment arm will be compared between arms to achieve one of the main objectives of the study.

## INTRODUCTION

Tinnitus is the perception of sound in the absence of an external auditory stimulus and is commonly described as 'ringing in the ears'. The condition significantly affects approximately 5-10% of the global population<sup>1-3</sup>. Tinnitus is heterogeneous with a diverse range of aetiologies but is believed to be commonly accompanied by a sensorineural hearing loss<sup>4-6</sup>. One ongoing hypothesis is that the decreased input into the peripheral auditory system due to hearing loss causes spatial reorganisation of the brain and/or compensatory changes in firing activity in multiple regions along the ascending auditory and non-auditory pathways that can lead to the tinnitus percept<sup>3 5 7 8</sup>.

In normal hearing individuals, sound travels as vibrations through the outer and middle ears into the cochlea, where cells within the cochlea convert the vibrations into neural signals that get transmitted along the auditory nerve to the brain<sup>9 10</sup>. The neural signals travel up through the brainstem, midbrain, and thalamus to the auditory cortex for sound perception. The ascending auditory pathway has a well-organised spatial map of frequencies (i.e., neurons located in a certain region respond best to a specific sound frequency and this spatial ordering of frequencies is known as tonotopy or a tonotopic map). In addition to the ascending pathway, there are dense descending connections from higher auditory and cognitive centres down to earlier stages of auditory neurons, which provide a way for sound perception to be modified or fine-tuned by attention and learning centres<sup>11-16</sup>. Furthermore, there are widespread projections from limbic and non-auditory pathways, such as somatosensory pathways, to the auditory network<sup>17-27</sup>.

In tinnitus patients, the abnormal reorganisation of the auditory brain can occur as spatial reorganisation of the tonotopic map and/or changes in neural firing in one or several of the auditory regions<sup>3 5 7</sup>. For example, a high frequency hearing loss could lead to a downregulation of peripheral synapses and activity in the high frequency region of the thalamus (e.g., medial geniculate body) and auditory cortex, in which those neurons then become more sensitive and active to lower frequency sounds (i.e., an expanded frequency

representation in the auditory brain for lower frequencies). Due to this frequency expansion and/or changes in firing patterns in those regions (e.g., hyperactivity or hypersynchrony across neurons), the patient experiences a phantom percept (tinnitus) corresponding to that expanded brain region. There are recent studies suggesting that topographic reorganization may not be necessary for tinnitus or phantom sensations in general<sup>28 29</sup>. It may be possible that the central auditory system more broadly overcompensates for the loss of peripheral input and increases the central gain in different networks of neurons along the ascending auditory pathway and in connection with multiple non-auditory brain regions to not only better sense the incoming sound that leads to excessive cortical activity reaching awareness but also integrating the emotional and cognitive/memory attributes with the phantom percept<sup>30 31</sup>.

The most commonly used approach for treating tinnitus is auditory stimulation, such as sound amplification (e.g., hearing aids) or sound therapy (e.g., noise-maskers, tone sequences or music therapy), which are intended to drive additional input into the auditory system and interact with the abnormal auditory neurons involved with tinnitus<sup>32-36</sup>. Based on extensive research in animals and several human studies, an emerging approach for driving strong plasticity and altering neurons within the auditory system is bimodal neuromodulation using acoustic stimulation combined with a non-auditory input, such as with vagus, somatosensory or trigeminal nerve stimulation<sup>20 37-45</sup>. Since somatosensory or trigeminal inputs can activate or modulate neurons throughout the auditory pathway<sup>20 23 24 27 46-52</sup>, combining sound stimulation with electrical stimulation of different locations on the body, especially via cranial nerves, has gained increasing interest in the tinnitus field as a promising approach for reversing the abnormal patterns of auditory neurons associated with tinnitus.

To date, there have only been a limited number of small and/or uncontrolled pilot studies to assess the safety and efficacy of bimodal neuromodulation approaches employing sound stimulation combined with cranial nerve stimulation for tinnitus treatment. These have included invasive vagus nerve stimulation<sup>41 53</sup>, non-invasive stimulation of the vagus nerve<sup>54-56</sup> and non-invasive cervical or trigeminal nerve stimulation<sup>42-44 46 47</sup>. While vagus nerve stimulation demonstrated promising results in animals<sup>37</sup>, human studies have shown mixed results<sup>41 53</sup>.

Published human studies using non-invasive cervical or trigeminal nerve stimulation have demonstrated promising initial efficacy <sup>42-44</sup>. However, these results should be considered preliminary as the data stems from small pilot studies. Therefore, progression to properly designed, sufficiently powered, blinded and randomised clinical trials are critically needed in the tinnitus field <sup>34 36 57 58</sup> and to further confirm the efficacy and safety of bimodal neuromodulation combining sound and cranial nerve stimulation.

This study protocol is part of a major clinical development program sponsored by Neuromod Devices (Dublin, Ireland) to provide large-scale clinical evidence of the safety and efficacy of a new bimodal neuromodulation treatment for tinnitus (using acoustic and trigeminal nerve stimulation; Figure 1). This study protocol is designed to confirm and enhance, through further stimulation optimization, the clinical efficacy demonstrated in a recently completed clinical trial (TENT-A1) evaluating bimodal neuromodulation in 326 tinnitus patients. The TENT-A1 protocol has been previously published <sup>59</sup> and listed on ClinicalTrials.gov (Identifier: NCT02669069). TENT-A1 was a double-blind, two-site randomised study that evaluated the relative efficacy and safety of three different settings for acoustic and trigeminal stimulation (i.e., different acoustic frequencies, electrical stimulation patterns on the tongue, and inter-modality delays). The treatment period was 12 weeks in which the therapeutic effects were assessed during treatment and at several follow-up visits up to 12 months post-treatment. Patients were presented with one stimulation setting for the entire 12-week treatment period. The positive results from TENT-A1 <sup>60</sup> have led to further questions and new directions for confirming and further optimising stimulation parameters for bimodal neuromodulation, which will be investigated through the protocol presented in this paper describing a follow-up double-blind, randomised clinical trial (TENT-A2) in 192 tinnitus patients.

### **Study objectives**

The primary objectives of TENT-A2 are to: (1) confirm the positive therapeutic effects, safety profile and patient tolerability observed in TENT-A1; (2) determine the therapeutic

effects of changing the stimulation parameters over time, in which the first stimulation setting is presented during the first 6 weeks of treatment and a second stimulation setting is presented during the second 6 weeks of treatment; and (3) assess how treatment outcome depends on the contribution of different acoustic or tongue stimuli not tested in TENT-A1. Secondary objectives include investigating the relative response of patient subtypes to the different treatment parameters. Building upon the data collected in TENT-A1, this study will allow for the continued collection and analysis of safety data.

## **METHODS AND ANALYSIS**

### **Trial design**

TENT-A2 is a prospective, single-site, parallel-arm, randomised, double-blind, comparative study investigating the safety and efficacy of four different treatment regimens. The treatment period evaluated is 12 weeks, in which different parameter settings will be delivered sequentially in the first and in the second 6-week segments of treatment (Table 1). Patient assessments will be performed at screening, enrolment (start of treatment), interim (after 6 weeks of treatment with the first stimulation setting), and end of treatment (after 6 weeks of treatment with the second stimulation setting). Post-treatment assessments will be conducted at 6-week follow-up, 6-month follow-up and 12-month follow-up (Table 2). TENT-A2 will be conducted at the Wellcome Trust-HRB Clinical Research Facility at St. James's Hospital in Dublin, Ireland. The protocol was independently reviewed and approved by Research Ethics Committees of the Tallaght Hospital - St James's Hospital (Reference: 2018-03-List 9). The trial is sponsored by Neuromod Devices. The trial was initially registered on ClinicalTrials.gov on 8 May 2018 (Identifier: NCT03530306). The first patient was enrolled on 20 March 2018 with the last assessment planned for June 2019. Our reporting follows standard protocol items for clinical trials defined in the SPIRIT 2013 Statement <sup>61</sup>.

## Eligibility criteria

Eligible patients will be aged 18-70 years at screening, self-report of experiencing predominantly tonal tinnitus for >3 months and ≤10 years, score from between 38 to 100 points on the Tinnitus Handicap Inventory (THI), have a wide-band noise Minimum Masking Level (MML) measurement between 20 and 80 decibels hearing level (dB HL), be able to read and understand English, be willing and able to provide informed consent, and be willing to commit to the full duration of the study.

Candidates will be excluded if they have objective tinnitus, pulsatile tinnitus (rhythmical sounds that often beat in time with the heartbeat), somatic tinnitus caused by a head or neck injury, or tinnitus that is comorbid with a neurological condition that may lead to loss of consciousness or is considered to be the dominant feature of the tinnitus as assessed by an audiologist or clinician. Conductive hearing loss demonstrated by abnormal otoscopy or abnormal tympanometry are exclusion criteria, as is a sensorineural hearing loss either unilaterally or bilaterally in which the subject has >40 dB HL in at least one measurement frequency in the range of 0.25-1.00 kHz or has >80 dB HL in at least one measurement frequency in the range of 2.0-8.0 kHz. Exclusions also include those patients who began wearing a hearing aid within 90 days prior to eligibility assessment, those with any type of electro-active implantable device (e.g., vagal nerve stimulator, cochlear implant or a cardiac pacemaker), and those with the following conditions that can be comorbid with tinnitus: Meniere's disease, loudness discomfort level for sounds presented <30 dB sensation level (SL), temporomandibular joint disorder (TMJ), and anxiety determined by a score >120 out of 160 on the state-trait anxiety inventory (STAI)<sup>62 63</sup>. Moderate to severe dementia as indicated by a score <20 on the mini-mental state examination (MMSE)<sup>64</sup> will also be sufficient reason for exclusion. A final set of exclusion criteria based on medical history taken at the screening assessment are: oral piercings, pregnancy, involvement in medico-legal cases, history of auditory hallucinations, current prescription of a drug for a central nervous system pathology (i.e., epilepsy, Multiple Sclerosis, Parkinson's, and bi-polar disorder), and previous use of a

Neuromod Devices' product. Finally, the patient may be excluded if the principal investigator does not deem the candidate to be suitable for the study for other reasons not listed above.

## **Intervention**

Patients enrolled in the trial will be given a proprietary CE-marked Class IIa medical device, which comprises bimodal auditory and trigeminal nerve stimulation from the sponsor company (Figure 1; Neuromod Devices, Dublin, Ireland). High-fidelity Bluetooth headphones deliver the auditory stimulation, which includes sequences of pure tones and/or wideband noise. The trigeminal nerve is stimulated electrically via a 32-electrode transmucosal array placed on the anterior dorsal surface of the tongue. Tongue stimulation is delivered in the form of biphasic anodic-leading pulses of between 5 and 130  $\mu$ s duration and fixed amplitude. The electrodes in the array are stimulated in a temporo-spatial pattern that represent features of the acoustic stimulus, such as the frequencies and onset of stimulus tones. Each stimulation setting listed in Table 1 represents a different combination of acoustic and tongue stimulation patterns and/or delays that are being evaluated in this study.

The patient's pure-tone audiometric thresholds (in the range 0.25 to 8 kHz) will be captured at the screening visit and subsequently used to configure the intensity of the auditory stimuli typically to 10 dB SL above their hearing thresholds. The patient will be provided with an option to adjust the default auditory stimulus intensities from -12 dB to +12 dB in 2 dB increments during treatment. For safety reasons, the upper level of stimulus intensity is limited for those patients with >70 dB HL hearing loss at any frequency. The treatment device reverts to the default stimulus intensities at the start of each new treatment session. Any adjustments made by the patients to the stimulus intensities are logged in the device's memory for subsequent analysis.

The tongue stimulus intensity will be configured for each patient at enrolment, based on a calibration procedure that determines the patient's threshold of perception. During treatment, the patient is also provided with the option to adjust the tongue stimulus intensity up to a maximum of 60% above the calibrated level, or down to a minimum of 40% below the

calibrated level, to allow patients to adjust for natural variances in somatosensory or perceptual sensitivity (e.g., due to variations in electrolyte concentrations in the saliva or relative dryness in the mouth).

Patient usage and stimulus adjustments are logged automatically by the device, such as the time and date when the device is in use, the duration of electrode contact with the tongue, and the intensities of both the auditory and tongue stimuli.

Each device will be programmed with the personalised settings and treatment regimen for each subject at the Sponsor's manufacturing site. The devices will be clearly identified with the patient's Unique Identifier Code (UIC). Investigators are extensively trained on fitting the device and instructing patients on its use per the manufacturer's instructions. Patients will be provided with a training session on how to use the device at the enrolment visit. A *Quick Start Guide* and a *User Manual* will be provided to each patient to take home. Before leaving the clinical site at the enrolment visit, patients will complete a supervised treatment session that is at least 15 minutes in duration to ensure they are competent and comfortable using the device.

### **Outcome Measures**

Subjective clinical outcome measures commonly used to assess tinnitus symptom severity are the Tinnitus Handicap Inventory (THI)<sup>65</sup> and the Tinnitus Functional Index (TFI)<sup>66 67</sup>. The THI provides a measure of the emotional and functional impact of tinnitus, in which 25 items are scored 4/2/0 on a categorical scale corresponding to yes/sometimes/no. The global score of the THI has a value from 0 to 100 with a higher score indicating a greater negative impact of tinnitus. The TFI assesses a range of tinnitus-related functional complaints experienced over the week prior to assessment. Each of the 25 items is assessed on an 11-point Likert scale, and the sum of the scores is normalised to give a global score from 0 to 100 with a higher score also indicating a greater negative impact. The Clinical Global Impression (CGI) is assessed at multiple visits to give an overall impression of the change in tinnitus (CGI-I) or sleep (CGI-S) since beginning treatment.

Tinnitus loudness is assessed by MML, tinnitus loudness matching (TLM), and a visual analogue scale (VAS). MML is a psychoacoustic estimate of the lowest level of wideband noise required to minimally mask the patient's tinnitus<sup>68</sup>. The stimulus is presented binaurally, after the patient's noise threshold level is obtained. TLM is assessed by presenting a 1 kHz tone contralateral to the predominant tinnitus ear or if tinnitus is equally loud in both sides or localised in the head, the stimuli is presented to the ear with better hearing<sup>69</sup>. The stimulus is increased until the patient confirms that it is equal in loudness to their tinnitus. A VAS is employed for patients to rate the current loudness (or annoyance) of their tinnitus with 0 equating to 'not loud at all' and 10 equating to 'extremely loud'<sup>70</sup>. Both investigator-administered (MML, TLM) and patient-reported assessments (VAS) are used because there is no agreed standard. While a tinnitus loudness rating performs better against acceptability criteria for reliability and validity than does a TLM or MML test, the rating question is limited because it is a single-item instrument and is probably able to detect only large changes<sup>71</sup>.

Patient-reported and investigator-reported adverse events (AEs) will be recorded, classified, coded and summarized. AEs will be classified according to severity, causality (treatment vs non-treatment related) and whether they are anticipated. They will be further coded by type for subsequent analysis, trending and reporting purposes. Any serious AEs will be reported to the local competent authority, the Research Ethics Committee and the Sponsor's Notified Body as required by local reporting regulations (under the Medical Device Directive 93/42/EC). The investigators will remain vigilant for signs of possible treatment-related changes in oral health (e.g., irritation, discomfort or disease in the oral cavity) and the impact of tinnitus.

Monitoring by non-patient facing investigators at the 6-week assessment will take place and the study may be stopped if the mean changes in THI or MML increase by 7 points or 5.3 dB, respectively. Treatment-related changes in hearing thresholds that will be considered an AE is a deterioration from screening to end of treatment of 15 dB in a minimum of two adjacent test frequencies (0.25-8 kHz) in either ear that cannot be explained by a conductive hearing problem or a recent excessive noise exposure. An additional safety endpoint will be that the

mean change in hearing thresholds across all patients does not worsen by more than would be expected due to age-related hearing loss.

Compliance data will be extracted from log files on each patient's device. Compliance rate will be expressed as a percentage of usage relative to (i) the expected compliance as per the intended use for the device (a total of 42 hours over the 6-week period and a total of 84 hours over the 12-week period), and to (ii) a predefined minimum acceptable compliance threshold (defined as at least 3 hours average usage within a 1-week period, corresponding to a sum total of 18 hours of treatment for the first 6-week period and 36 hours of treatment for the full 12-week period).

## **Recruitment**

Patients will be recruited primarily via regional and national radio advertising that directs patients towards a dedicated trial sign-up website ([tinnitustrials.ie](http://tinnitustrials.ie)). The recruitment website provides information on the study and how to proceed with registration. To register their interest, candidates must enter their email address so that they can be provided, via email, with a UIC and Personal Identification Number (PIN) as well as a link to an online eligibility assessment (hosted by SurveyGizmo). To access the online eligibility assessment, candidates must click the link which brings them to a log in page that requires them to input their UIC and PIN. Once logged in, candidates can find further details about the requirements of participating in the study. Candidates will answer a set of general pre-screening questions on age, duration of tinnitus, oral piercings, other current medical conditions and other eligibility criteria-related questions. The online eligibility assessment is intended to reduce the burden of performing detailed screening visits on a large number of candidates who are expected to be interested in the trial yet would not satisfy the inclusion and exclusion criteria. Candidates who meet the inclusion criteria will be provided with a patient information leaflet and informed consent via email or post and invited to a screening visit at the Wellcome Trust-HRB Clinical Research Facility at St. James's Hospital in Dublin, Ireland.

## Study timeline

Patients are expected to visit the clinic seven times throughout the entirety of the study. They will also receive two compliance telephone calls during the device usage period, one during the first six weeks and the other during the second six weeks of treatment. The schedule of clinical research activities is illustrated in Table 2. The various assessments are completed by a multi-disciplinary team including audiologists, medical doctors, physiotherapists, research nurses, and clinical investigators.

The screening visit will be used to determine whether a patient is eligible for enrolment into the trial as defined by the previously detailed inclusion and exclusion criteria. The initial objective of the screening visit is to obtain written informed consent, in which the patients will be given sufficient time to read through the patient information leaflet and informed consent form. Initial outcome measure assessments, patient characteristics, and audiological profile are also obtained at the screening visit. This information is employed in the subtype classification of patients, the stratified random allocation process, and for device configuration as described below.

At the enrolment (device fitting) visit, a physiotherapist conducts a comprehensive assessment comprising a set of 25 predefined cranial manipulations designed to diagnose somatic tinnitus<sup>26</sup> as well as five additional manoeuvres of the tongue. Somatic tinnitus is defined in this study as tinnitus where at least one of the somatic manipulations reliably produces a change in any psychoacoustic characteristics of a patient's tinnitus (e.g., in pitch, loudness, or localisation). Assessments of outcome measures previously assessed at the screening visit are repeated at the enrolment visit. The enrolment visit also entails an oral health examination, device training and deployment, and a supervised treatment session. The treatment is self-administered by the patient daily for two 30-minute sessions over the course of the treatment. These sessions can be contiguous or at completed at different times of the day.

The outcome measure assessments and safety information collection are repeated at the interim visit, half way through the 12-week treatment. Compliance data will also be assessed

and reviewed at the interim visit. Patients with poor compliance will be encouraged to improve their treatment device usage.

The assessments will be repeated at the endpoint visit (i.e., end of 12-week treatment) including the outcome measure assessments and the oral health examination. An exit interview will be completed and the device will also be retrieved at the endpoint visit. Three follow-up visits up to 12 months will be conducted to assess the post treatment effects of the intervention.

### **Sample size**

Arm 1 and Arm 2 are powered to detect a between-arm clinically meaningful difference in the mean THI changes from enrolment to interim, where the clinically meaningful change in THI is considered to be 7 points <sup>72</sup>. The assumed sample standard deviation is 12 points, as estimated from a previous study sponsored by Neuromod Devices (TENT-A1, <sup>60</sup>). The sample size calculations were performed using Matlab 2016a, assuming a two-sided significance level of 0.025 (pairwise t-test), and power of 90%, resulting in a total of 75 patients to be enrolled in treatment Arm 1 and Arm 2. The remaining 0.025 of the overall 0.05 significance level is retained for within-arm and subgroup hypothesis tests.

Arm 3 and Arm 4 are included for exploratory endpoints and are powered to detect a between-arm 10-point THI difference compared to Arm 1 from enrolment to interim. This requires approximately 15 patients in Arm 3 and Arm 4. Therefore, the allocation ratio among treatment arms is 5:5:1:1. In total, 180 patients (75+75+15+15) will be required to complete the interim assessment (first 6-weeks of treatment) across the four arms of the study. The attrition rate for the first 6 weeks of treatment in TENT-A1 was approximately 7%. Therefore, it is estimated that approximately 193 patients would need to be enrolled to ensure 180 patients complete the 6-week treatment assessment. This is rounded to 192 patients to ensure balance at the required ratio (5:5:1:1).

## **Allocation**

Eligible patients will be randomised, as per the allocation ratio previously described (5:5:1:1), between the four parallel treatment arms (Table 1). Stratified randomisation using the method of Minimisation<sup>73</sup> will be performed to balance the influence of several baseline covariates in the post-hoc analyses. The stratification covariates are chosen based on the investigator's research objective to elucidate relative treatment effects on possible subtypes of tinnitus patients with varying underlying characteristics. Allocation of patients will be stratified across the four intervention arms based on findings from TENT-A1 and in ranked order as per the following strata: (i) hyperacusis <70 dB SL @500Hz, (ii) hyperacusis <60 dB SL @500Hz (note that the Loudness Discomfort Level assessment is used as an indicator for hyperacusis), (iii) high THI of >56 points at screening, (iv) unilateral tinnitus as assessed at screening, and (v) participants who do not fall into the previous categories (note that this stratum will not be used for inferences purposes).

## **Data Collection**

All data will be collected electronically using a validated electronic clinical Case Report Form (eCRF) application. Patient data collected at all stages of the trial will be entered into the eCRF using UICs assigned to patients at recruitment phase. All patients and investigators performing the patient evaluations will be blinded to allocation arm and no allocation information will be contained in the eCRF. The data monitors will be able to remotely view the blinded data in the eCRF to monitor safety data.

## **Statistical Methods**

The primary efficacy analyses will focus on investigating: (i) within-arm (Arm 1) changes in THI and TFI from baseline (average of screening and enrolment) to interim (first 6 weeks of treatment) and (ii) between-arm (Arm 1: Arm 2) changes in THI from enrolment to interim. The initial study phase for the between-arm inferences is enrolment to minimise confounding

factors as far as possible, while the initial study phase for within-arm analyses is the average of screening and enrolment to match the design of TENT-A1 and so that the reported changes are reflective of actual clinical practice. All primary efficacy analyses will be controlled at an overall significance level of 0.05 using a graphical-based sequential/parallel testing procedure with fallback <sup>74</sup>. The between-arm analyses will be based on an intention-to-treat estimand and tested with multiple regression using enrolment scores as a covariate. Missing data will be handled by using Markov chain Monte Carlo multiple imputation methods <sup>75 76</sup>. The within-arm analyses will be based on a per-protocol estimand and tested with paired two-tailed t-tests. The use of per-protocol estimand will ensure that the changes in outcome measures within each treatment arm are reflective of real-use scenarios, that is, where the patients use the treatment as directed. The threshold for inclusion in the per-protocol analysis is set at the predefined minimum acceptable compliance threshold previously described.

Secondary and exploratory efficacy analyses will be conducted to evaluate further improvements on the within-arm changes in THI from interim to end of treatment due to the use of different stimulation settings over time, therapeutic effects in different subtypes of tinnitus patients described previously and sustained effects by analysing changes in efficacy outcome measures from end of treatment to the three follow-up assessments (i.e., at 18, 38 and 64 weeks after device fitting). Similar assessments performed for THI will be performed for TFI as additional analyses.

Safety analyses will be performed by evaluating the incidence and expectedness of AEs, classified as treatment or non-treatment related, and further sub-classified according to severity. AEs will be recorded proactively by monitoring significant deteriorations in THI, TFI, MML, hearing thresholds and oral health, and reactively by documenting any AEs reported by patients during the study. All AEs will be analysed for trends.

Efficacy and safety data analysis will be conducted in compliance with the Consolidated Standards of Reporting Trials guidelines for randomised trials <sup>77</sup>.

## **Dissemination**

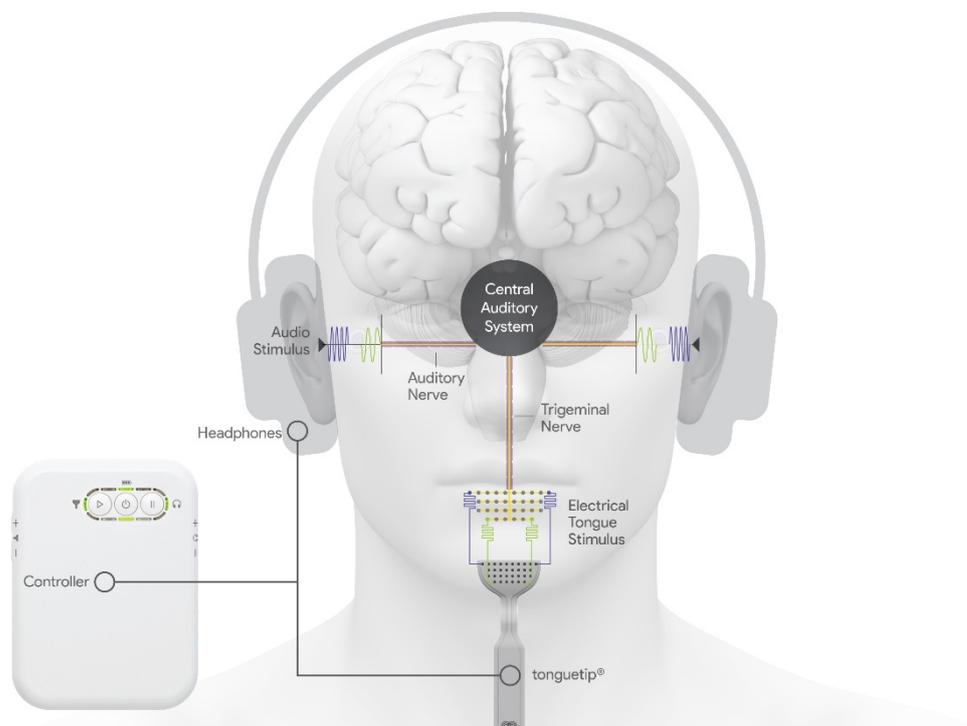
Findings will be distributed to relevant scientific, academic, clinical, health service and patient communities through publications in peer-reviewed and high impact scientific journals as well as via seminars and talks at conferences.

## **DISCUSSION**

This paper outlines the protocol for a prospective single site, parallel-arm, randomised, double-blind, comparative study designed to confirm the safety, efficacy and patient tolerability of bimodal neuromodulation for tinnitus treatment observed in the previous TENT-A1 trial, as well as to determine the therapeutic effects of adjusting the treatment stimulation settings over time and identifying responsive subtypes of tinnitus patients.

This study is important for the tinnitus field for several reasons. First, the findings in TENT-A2 can be compared to those obtained in TENT-A1 to assess if the safety and efficacy of bimodal neuromodulation treatment for tinnitus can be confirmed. Replication of clinical trial results is critically needed to build confidence in a field that is currently plagued with scepticism towards new types of treatment methods. Second, there are still only a few large-scale blinded and randomised clinical trials for tinnitus treatment in which low quality clinical trial design and reporting has been identified as a major barrier to developing effective therapies<sup>58 78 79</sup>. This study will not only provide valuable insight into the safety and efficacy for different parameter settings of bimodal neuromodulation for tinnitus patients, but it will also contribute to the establishment of higher clinical standards for evaluating different tinnitus treatments than is currently practised. Third, there is a movement in the clinical realm towards personalized medicine and in optimizing treatments per each patient. The design of this study may reveal specific stimulation features and temporal effects of treatment for driving greater improvements in tinnitus in different subtypes of patients and will help move the field towards more reliable treatment outcomes.

**Figure 1.** Bimodal sensory neuromodulation device for tinnitus treatment. The system developed by Neuromod Devices (Dublin, Ireland) consists of wireless high-fidelity circumaural headphones that deliver acoustic stimuli, a 32 electrode array for presenting electrical stimulus patterns to the anterior dorsal surface of the tongue, and a battery-powered *Controller* that coordinates both stimulus modalities.



**Table 1.** Stimulation parameter settings that will be utilised for the four parallel treatment arms of the TENT-A2 study. Two different stimulus settings will be used for each treatment arm during the first and second 6-week periods of the 12-week treatment. Labels listed in the table are specific names used internally in the company. PS1 is an equivalent stimulus setting used in the previous TENT-A1 study to assess repeatability of results between two different studies. PS1 consists of a sequence of tones mixed with structured wideband noise, in which the tones are synchronised in time with electrical pulses presented to the tongue (for further details, see published protocol paper for TENT-A1<sup>59</sup>). One or more acoustic or electrical features in PS1 are modified or removed to create the other proprietary stimulus settings used in the TENT-A2 study.

Treatment	First 6-weeks	Second 6-weeks
Arm 1	PS1	PS4
Arm 2	PS6	PS10
Arm 3	PS7	PS4
Arm 4	PS9	PS6

**Table 2.** Schedule of visits, tasks and assessments for TENT-A2 study (wks: weeks).

	Screening	Enrolment and Fitting	Post-Allocation				Follow-Up	Follow-Up	Follow-Up
	Screening	Enrolment	Telephone Call	Interim Visit	Telephone Call	Endpoint Visit			
TIMEPOINT	<i>t - 8wks</i>	<i>t = 0</i>	<i>t + 3wks</i>	<i>t + 6wks</i>	<i>t + 9wks</i>	<i>t + 12wks</i>	<i>t + 18wks</i>	<i>t + 38wks</i>	<i>t + 64wks</i>
<b>TASKS:</b>									
Eligibility Screen	X								
Informed Consent	X								
Allocation		X							
Training on Using the Device		X							
Review of Device Usage Data				X					
Encourage Patient Compliance		X	X	X	X				
Return Device						X			
<b>INTERVENTIONS:</b>									
Arm 1		X	X	X	X	X			
Arm 2		X	X	X	X	X			
Arm 3		X	X	X	X	X			
Arm 4		X	X	X	X	X			
<b>ASSESSMENTS:</b>									
Medical History	X					X			
Medications or Illnesses	X	X		X		X	X	X	X
Audiometric Test of Hearing	X					X			
Tinnitus Location & Tonality	X	X		X		X	X	X	X
Tinnitus Loudness Matching	X								
Loudness Discomfort Level	X	X		X		X	X	X	X
Mini-Mental State Examination	X								
State-Trait Anxiety Inventory	X								
Somatic Assessment		X							
Oral Assessment		X				X			
Minimum Masking Level	X	X		X		X	X	X	X
Pittsburgh Sleep Quality Index	X	X		X		X	X	X	X
Tinnitus Handicap Inventory	X	X		X		X	X	X	X
Tinnitus Functional Index	X	X		X		X	X	X	X
Visual Analogue Scales	X	X		X		X	X	X	X
Hyperacusis Questionnaire		X		X		X	X	X	X
Clinical Global Impression				X		X		X	X
Adverse Events		X		X		X	X	X	X
Device Usability Questionnaire						X			
Demographic Data							X		

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