Single versus Combination Treatment in Tinnitus: An International, Multicentre, Parallel-arm, Superiority, Randomised Controlled Trial

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Abstract

This international multicentre, parallel-arm, superiority, randomised controlled trial investigated whether combination therapies are superior to single interventions in the treatment of chronic subjective tinnitus. Tinnitus patients were recruited from five clinical sites across the EU and randomly assigned using a web-based system, stratified by their hearing and distress level, to single or combination treatment of 12 weeks. Cognitive-behavioural therapy, hearing aids, structured counselling (app-based), and sound therapy (app-based) were administered either alone or as a combination of two treatments resulting in ten treatment arms. The primary outcome was the difference in the change from baseline to week 12 in the total score of the Tinnitus Handicap Inventory (THI) between single and combination treatments in the intention-to-treat population. All statistical analysis were performed blinded to treatment allocation. 674 patients of both sexes aged between 18 and 80 years were screened for eligibility. 461 participants (190 females) with chronic subjective tinnitus and at least mild tinnitus handicap were enrolled, 230 of which were randomly assigned to single and 231 to combination treatment. Least-squares mean changes from baseline to week 12 were -11.7 for single treatment (95% confidence interval [CI], -14.4 to -9.0) and -14.9 for combination treatments (95% CI, -17.7 to -12.1), with a statistically significant group difference (p=0.034). Cognitive-behavioural therapy and hearing aids alone had large effect sizes, which could not be further increased by combination treatment. No serious adverse events occurred. In this trial involving patients with chronic tinnitus, all treatment arms showed improvement in THI scores from baseline to week 12. Combination treatments showed a stronger clinical effect than single treatment, however, no clear synergistic effect was observed when combining treatments. Instead, we observed a compensatory effect, where a more effective treatment offsets the clinical effects of a less effective treatment. ClinicalTrials.gov Identifier: NCT04663828.

Introduction

Tinnitus is defined as "the conscious awareness of a tonal or composite noise for which there is no identifiable external acoustic source",[1] with an estimated prevalence of 14.4% (95% confidence interval [CI], 12.6 to 16.5) in the global population, with 2.3% (95% CI, 1.7 to 3.1) being severely affected.[2] Severe tinnitus is associated with emotional stress, cognitive dysfunction, and/or autonomic arousal, leading to maladaptive behavioural changes and functional disability.[1]

Numerous causes and risk factors for tinnitus have been identified,[3] whereby peripheral and central mechanisms are involved in its emergence and maintenance, exemplified by pathological alterations in the ear, along the auditory pathway[4], as well as in non-auditory brain regions.[5] There is a broad spectrum of aetiologies, phenotypes, and underlying pathophysiological mechanisms of tinnitus. Many adults with chronic tinnitus report having tried multiple tinnitus treatments before finding a treatment that reduces their tinnitus distress.[6] Despite the availability of treatment guidelines,[7,8] clear guidance on which treatment strategy is best for the individual patient is not yet available. A viable option for clinical management could be the combination of different treatment options to target various facets of this symptom simultaneously.

However, studies on the effectiveness of combining clinical interventions are scarce.[9–11] Prominent examples of combining different treatment types are represented by the combination of acoustic therapy with directive counselling as implemented in the Tinnitus Activities Treatment[12] or the Tinnitus Retraining Therapy.[13]

The primary objective of the current trial was to investigate if combination treatments are more effective than single treatments for patients with chronic tinnitus. Four established treatment strategies were selected: cognitive-behavioural therapy (CBT), hearing aids (HA), structured counselling (SC), and sound therapy (ST).[14] Participants were randomised either to a single treatment out of this set of treatments or to a combination of two treatments. Further, we attempt

to overcome methodological weaknesses[15] of previous trials by investigating a large multinational sample of tinnitus patients, using harmonised patient selection and screening procedures, as well as standardised interventions and assessments.

Results

Between Apr 16, 2021, and Sept 20, 2022, 674 persons with tinnitus were assessed for eligibility, of whom 461 (68.3%) fulfilled the inclusion criteria and consented to participate. After randomisation, 230 were allocated to single treatments and 231 were allocated to combination treatments (Figure 1).

The initial planned sample size for the trial was 500 patients.[16] Since our study plan required a recruitment of an exact number of patients with specific tinnitus profiles (eligibility criteria and stratification proceedings), plus the trial was performed during the COVID-19 pandemic with country-specific hospital policies, recruitment and inclusion processes lasted longer than expected. Hence, we closed the trial in December 2022 with N = 461 included and treated patients, in order to keep to the schedule of our funding period (Granada: 89, Athens: 99, Leuven: 74, Regensburg: 100, Berlin: 99). A post hoc power computation indicates that with a two-tailed alpha level of less than 5%, the available sample size of N = 461 provides our trial with 79.5% power to detect an effect size of 0.26.

Table 1 shows the baseline characteristics by treatment arm. Mean baseline THI total scores were 48.5 (SD 19.5) in the single treatment group and 47.4 (SD 19.9) in the combined treatment group. Except for age and hearing aid indication, the baseline characteristics were generally well balanced between the treatment arms (see Table 1 and Table S6). Both age and hearing aid indication were considered as covariates during statistical analyses. The difference in hearing aid indication results from randomising only individuals with relevant hearing loss to HA treatment arms. Results of audiometric measurements are shown in Figure S2 and S3.

Participants' baseline characteristics were similar to the group of persons with tinnitus seeking medical help in the general population (Table S7).

Regarding the primary objective, the least-squares mean change from baseline to week 12 in the THI total score was -11.7 (95% CI -14.4 to -9.0) for the single treatment groups and -14.9 (95% CI, -17.7 to -12.1) for the combination treatment arms (see Figure 2 & Table 2) (interaction effect [single vs. combination treatments at final visit vs. baseline] β = 3.2, 95% CI, 0.2 to 6.1, p = 0.034).

Model parameters and model assumptions for the primary objective can be found in Table S8 and Figure S4. The least-squares mean change from baseline to week 12 in the THI total score for the single vs. combination treatment comparison for each treatment strategy is reported in Table 2, and separately for every treatment arm in Table 3 and Figure S5; and further separated by hearing aid indication in Table S9 and tinnitus severity in Table S10. Figure 2 shows least-squares mean changes from baseline to interim visit at week 6, final visit at week 12, and follow-up at week 36 for both the overall and individual single-combination treatment comparison. The results of the remaining objectives (as outlined in the SAP)[17] and time points (interim visit and follow up) are reported in Tables S11 – S13. Country-specific changes for the THI from baseline to final visit for single and combination treatment as well as for all treatment arms can be found in Table S14.

Regarding the secondary outcome measures, least-squares mean change from baseline to week 12 for TFI, Mini-TQ, PHQ-9, WHO-QoL, and NRS (all objectives) are shown in Tables 2 and 3 as well as Tables S15 – S27. Results of CGI-I are reported descriptively for single and combination treatment groups at final visit, see Figure S6 & S7, and separated by hearing aid indication (Figure S8) and tinnitus severity (Figure S9).

No SAE was evident in any patient. AEs appeared in 49 (21.3%) participants in single treatment groups, and in 49 (21.2%) participants in combination treatment groups. The most relevant AEs reported by patients were worsening of the tinnitus percept (6); worsening of their

psychological health (3); sleep problems (2); pain in the ear when wearing the hearing aid (1), ear infection (1), inflammation of the ear (1), dizziness (1), and mild transient hearing loss (1). Worsening of tinnitus symptoms is a relative common side-effect in tinnitus studies, as patients are focussing their attention more intently on their tinnitus to evaluate potential changes in tinnitus characteristics. Given the absence of any SAE and the low number of adverse reactions associated potentially with the various treatments, the present intervention types can be considered as safe. As AEs were rather rare and not severe, we abstained from analysing the strength of the relationship with treatment interventions and from documenting the time course of the reported AEs. A full listing of all AEs per treatment arm is provided in Table S28. Information on treatment adherence is given in Figure S1 and Table S29.

Pairwise post-hoc contrasts for the THI least-squares mean change revealed statistically significant (Bonferroni adjusted) differences between ST and CBT, ST and CBT+SC, ST and CBT+ST, ST and HA, and ST and HA+SC. For all other treatment contrasts, no statistically significant differences were found (all p-values > 0.050). Statistical parameters for all post-hoc contrasts are listed in Table S30. Sensitivity analyses of our primary outcome using no imputation and the method of Last Observation Carried Forward yielded similar results as our ITT analysis. However, under the assumption that data is not missing at random, our ITT findings cannot be upheld (Table S31 – S32). PP findings were different for the overall single vs. combination contrast (no statistical superiority of combination treatment; β = 2.8, 95% CI, -1.6 to 7.2, p = 0.206) (Figure S10, Tables S33 – S34). Exploratory analysis included the effect size estimates Cohen's d for all treatment arms which are shown in Table 3 and Figure 2.

Discussion

In this randomised trial on chronic tinnitus, the effectiveness of established tinnitus treatments (cognitive-behavioural therapy (CBT), hearing aids (HA), structured counselling (ST), and sound therapy (ST)) applied either alone or as a combination of two treatments was

investigated. All treatments were safe and the improvement in THI scores from baseline to week 12 was statistically stronger for combination compared to single treatment. However, a more detailed analysis of our data by pairwise post hoc comparisons of the various treatment arms suggests that the additional effect of a treatment combination depends on the effectiveness of a single treatment. In the case of ST, a clear superiority in favour of combination treatment was present, with the combination CBT+ST being statistically superior to single ST. Importantly, there was no statistically significant difference between CBT alone and CBT+ST. This finding shows that combining a treatment with low effectiveness (in this case ST) together with a treatment of high effectiveness (in this case CBT) does not lead to a simple regression to the mean.

Rather the high-effectiveness treatment counterbalances the effect of the low-effectiveness treatment and elevates the clinical improvement up to a level comparable to the single high-effectiveness treatment. Together with the observation that ST was the treatment which demonstrated the smallest improvements in tinnitus-related handicap (statistically significant less than CBT, HA, CBT+SC, CBT+ST, HA+SC), the additional beneficial effect of a treatment combination appears to depend on how effective a single treatment already performs. For the single treatment arm with ST, we observed a weak effect size of 0.24 (confidence interval [CI], -0.02 to 0.53) while combinations of treatments including ST yielded medium to strong effect sizes: SC+ST (Cohen's d = 0.71, CI, 0.46 to 1.02), HA+ST (Cohen's d = 0.78, CI, 0.43 to 1.37), and CBT+ST (Cohen's d = 0.80. CI, 0.55 to 1.12), which is driven by the combination treatments of higher effectiveness.

The weak clinical effectiveness of sound treatment alone is in line with previous work where sound treatment was used as an active control.[18,19] This trial shows that combining a treatment of weak clinical effectiveness with a treatment of stronger clinical effectiveness counterbalanced the weak effect and provokes a clinical improvement comparable to the

stronger effect. On the other hand, if a single treatment is already effective, a combination might not result in a synergistic effect.

Previous investigations evaluated combination treatments for tinnitus as well.[9–11] For instance it was demonstrated that Tinnitus Retraining Therapy,[13] which combines a specific acoustic therapy with directive counselling, reduced tinnitus symptoms more effectively than counselling alone.[9]

This is the first systematic trial to investigate CBT, HA, ST, and SC within the scope of one investigation. CBT approaches demonstrate the best body of evidence so far and are thus recommended by current treatment guidelines.[7,8,20] Of today, the recommendation for HAs is restricted to the treatment of concomitant hearing loss, and there is no recommendation for ST due to a lack of clear scientific evidence.[21–23] Counselling is recommended in form of information about tinnitus and the learning of potential coping strategies. However, counselling is usually not systematically structured and not investigated as such.[24]

With the present trial, we can directly put into perspective the effect size of CBT as the most established evidence-based treatment in tinnitus,[7,8,20,25,26] with HA, ST, and SC (ST and SC provided with mobile applications) as well as their combinations as treatment options for tinnitus. Further, the present trial provides the first large-scale evidence for HA and SC (administered as stand-alone treatments), with a clinical effectiveness on a similar level as CBT.

In view of the interpretation of the present findings for HAs, it is important to point out that the primary focus of a HA is on reducing hearing impairment by amplification of peripheral sounds and that this benefit could be conflated with an amelioration in tinnitus-related symptoms.

In a separate analysis by Schiele et al., data from our HA single treatment arm was used to investigate whether tinnitus frequency, hearing loss, HA-usage duration or the accuracy of HA fitting might serve as a predictor for treatment response. None of the mentioned variables predicted an improvement in tinnitus-related distress (THI, TFI) or subjective tinnitus loudness.[27]

The combination of HA+SC, which provided the strongest effect size in our trial, has not been investigated so far, and data about the clinical effectiveness in tinnitus are not yet available.[21,22] It should also be considered that we worked with a selected set of four tinnitus treatments and combinations of only two treatment types. Thus, it remains unknown, whether the combination of other treatment sets or combinations of three or more treatment types would lead to additional treatment benefits. Any interpretation of our findings should keep in mind, that we investigated specific applications of CBT, HA, ST, and SC. Potential reasons for the low efficacy of ST and SC in the present trial might include its self-administration, the limited interaction with a clinical specialist and/or the absence of specific instructions (stimulus, loudness, duration etc.). Thus, our conclusions on ST and SC might not be directly applied to a traditional clinical setting, where patients are not necessarily followed-up.

The duration of treatment was 12 weeks in all treatment arms. Meaningful clinical improvements were observed in most treatment arms after 6 weeks and improved further towards the final assessment after 12 weeks and remained during the follow-up period.

Despite the usage of interventions allowing for a high level of patient flexibility (SC and ST via mobile applications, HA), treatment compliance/adherence was low (see Figure S1 and Table S29) and dropout rates were high in our trial (per-protocol (PP) sample of 185 patients). CBT treatment arms, which require a high level of commitment with several on-site visits, demonstrated the highest proportion of dropouts in our trial, which potentially limits the interpretability and robustness of our CBT findings, as non-responders may be overrepresented among dropouts. In another recent study, in which CBT was compared with Neurofeedback, the CBT dropout rate was in a similar high range like in our study.[28] There is a large body of evidence in the literature that CBT is effective in the treatment of tinnitus (for an overview see the Cochrane review by Fuller et al., 2020),[25] and has been recommended in European guidelines for the management of tinnitus.[8] However, all studies investigating CBT alone might be susceptible to a selection bias, as only patients with motivation for CBT would have been

279 enrolled. The relatively high dropout rate of CBT in studies comparing various treatment
280 options reflects the clinical experience of the real-world situation where a relevant subgroup of
281 patients is not willing to undergo CBT. Detailed information on dropout reasons per treatment
282 arm are listed in Tables S2 – S5.
283 With the application of two treatments in combination, the chances that one or even both
284 treatments are not conducted as intended are increasing. The lack of monitoring, strict guidance,
285 or outpatient care in the case of SC, ST and HA, might be further potential reasons for treatment
286 non-adherence. Furthermore, high dropout rates are a well-known issue in mobile health
287 interventions.[29] Another reason could be that patients were randomized to treatments and did
288 not receive the treatment they desired. Under ideal treatment compliance/adherence (PP
289 analysis), we observed no overall superiority of combination treatments.
290 A potential explanation for this incongruency between intention-to-treat (ITT) and PP analysis
291 might be that under perfect conditions (PP), a single treatment which is conducted properly is
292 already effective on its own and thus there is no clear additional beneficial effect of a
293 combination treatment. However, if one or two treatments are not properly conducted (ITT), as
294 it is most probably the case in the everyday clinical treatment of tinnitus, a combination of
295 treatments provides an additional benefit. Our results indicate that there is a high need for
296 further research to better understand the clinical benefits of combination treatment; to get more
297 profound insights behind the reasons for low treatment adherence; and in approaches to increase
298 treatment adherence in daily clinical practice, such as the implementation of behavioral change
299 techniques or more extensive patient education.
300 A control group was not included in this trial, as the answer to the main question (comparison
301 of single and combined treatment) did not require a control group. Nevertheless, a control group
302 may have been helpful as an anchor for comparison with the ten treatment arms. However, our
303 results of CBT as single treatment correspond very well to meta-analytic data of its efficacy[25]
304 and thus provide an anchor for a well-established evidence based treatment approach. Further,

our data demonstrates low effectiveness of ST as a single treatment, supporting its use as an active control condition in randomised controlled trials.[18,19] Thus, the two treatment arms CBT and ST can be considered as reliable reference anchors for the interpretation of the results of the other 8 investigated treatment arms. Even though in 18% of all participants data of the primary outcome (THI) was missing, the sensitivity analysis using no imputation came to similar findings, which was further corroborated by applying the Last Observation Carried Forward approach. Yet, under the assumption of "missing not at random" and after conducting additional robustness evaluations using three different reference-based imputation methods, our findings cannot be sustained (see Tables S31-S32).

In this trial involving adults with chronic tinnitus, we found that 12 weeks of treatment with CBT, HAs, SC, or ST applied as single or in combinations of two treatments led to an amelioration in tinnitus-related handicap. There was no unambiguous synergistic effect of treatment combination, rather a compensatory effect, where a more effective treatment offsets the clinical effects of a less effective treatment. In clinical situations where it is unclear which treatment will benefit the particular patient, a combination of treatments might help to increase the chances of treatment success.

Methods

Study design

This was an investigator-initiated, international, multicentre, parallel-arm, superiority, randomised controlled clinical trial conducted in five hospitals across four European countries (Leuven, Belgium; Berlin and Regensburg, Germany; Athens, Greece; and Granada, Spain; see Table S35 in the Supplementary Appendix) as part of the UNITI project (Unification of Treatments and Interventions for Tinnitus Patients).[30] Included patients received treatment between April 2021 and December 2022. Detailed information about the trial rationale, design, methodological approaches, and statistical analysis strategies are published in the study

protocol and statistical analysis plan (SAP).[16,17] The study was approved by local ethics committees at every clinical site independently (combined ethical approval for German sites; please find the ethical approval documents in the Supplementary Appendix). Further, all authors vouch for the completeness and correctness of the data, adherence of the trial to the study protocol,[16] as well as adherence of data analysis strategies to the SAP.[17] A detailed list of author contributions can be found in Table S36 in the Supplementary Appendix. Written informed consent was obtained from all eligible patients prior to trial participation. For the preparation of this report we used the CONSORT guidelines (Consolidated Standards of Reporting Trials).[31]

Participants

Adults of both sexes (self-reported) aged between 18 and 80 years with chronic subjective tinnitus (lasting for six months or more) were recruited and screened at each clinical site. Inclusion criteria for trial participation were at least mild tinnitus handicap according to the Tinnitus Handicap Inventory[32] (THI; score ≥ 18) and tinnitus as primary complaint. Exclusion criteria were: presence of a mild or worse cognitive impairment according to the Montreal Cognitive Assessment[33] (MoCa; score ≤ 22); any relevant ear disorders or acute infections of the ear; one deaf ear; severe hearing loss (inability to communicate properly) as well as serious internal, neurological, or psychiatric conditions. Existing drug therapies with psychoactive substances had to be stable, and no start of any other tinnitus-related treatment in the last three months before trial participation was allowed. A detailed list of all eligibility criteria can be found in the trial protocol.[16] Written informed consent was obtained from all participants.

Randomisation and blinding

After successful on-site screening, eligible participants were stratified in four equally sized strata based on their THI total score (low [< 48] and high [≥ 48] tinnitus-related handicap) and

hearing aid indication (yes and no, criteria for hearing aid indication: Table S37). Criterion for low and high tinnitus-related handicap was defined based on historical data obtained from 837 patients at the clinical site in Regensburg with a median THI score of 48. Hearing aid indication criteria were specified by a group of international experts in the fields of audiology and otolaryngology (see Table S38). Participants were then randomised to one of ten treatment arms comprised of single (CBT, HA, SC, ST) and combination interventions (CBT+HA, CBT+SC, CBT+ST, HA+SC, HA+ST, SC+ST) under consideration of the stratification group. Patients from the two strata without hearing aid indication were not randomised in treatment groups that comprised HA treatment. The stratification according to tinnitus-related handicap was performed to ensure an equal representation of patients with high and low tinnitus distress in different treatment arms and thus avoid potential misinterpretations of our findings due to large differences in baseline tinnitus severity across treatment arms. Randomisation was conducted at each clinical site with an interactive web response system developed together with biostatisticians from the contract research organization Excelya (www.excelya.com). Excelya was further responsible to monitor all randomisation proceedings. Treatment codes were used to ensure blindness of the statistical analysis team to the type of treatment patients received. Unblinding was conducted after analyses completion. Patients and investigators/assessors were not blinded. See study protocol and statistical analysis plan for more detailed information.[16,17]

Procedures

Single and combination treatments were applied over a 12-week treatment phase. All treatment procedures were designed by dedicated experts in their respective fields (see Table S38 for expert team per treatment type) and described in detail in the study protocol.[16] To ensure consistency with respect to treatment and assessment implementation across clinical sites, workshops were held, and Standard Operation Procedure documents were created. Two of the

four treatment types were unguided, app-based therapies, minimising potential differences. HA fitting was standardised, and CBT was co-developed specifically for this trial.

CBT was based on the concept of fear-avoidance using exposure therapy.[34,35] The exposure exercises were delivered by trained psychologists or psychotherapists in weekly face-to-face group sessions (1.5-2 hours weekly; 12 weeks; group size: six to eight participants). For HA treatment, behind-the-ear hearing instruments (Type Signia Pure 312 7X; Sivantos Pte. Ltd., Singapore, Republic of Singapore/ WSAudiology, Lynge, Denmark) were fitted bilaterally with all noise-related signal processing deactivated by audiologists or HA acousticians according to the National Acoustic Laboratories-Non-Linear 2 generic amplification proceeding.[36] SC and ST were self-administered on a daily basis via a dedicated UNITI mobile application, which was available for Android and iOS devices as well as free of charge.[37] SC was oriented on recent European guidelines for tinnitus management[8] and consisted of 12 chapters featuring structured patient education (e.g., facts about tinnitus, brain and sound perception; myths and misconceptions about tinnitus; diagnosis of tinnitus; special types of tinnitus; therapeutic approaches; psychological and behavioural aspects) and tips on how to handle tinnitus distress. ST included 64 different artificial and naturalistic sounds with various state of the art modulation or filter techniques. Loudness and length of the sounds was adjustable by the patients. There are many different SC and ST approaches administered by clinicians. For clarity, we want to mention that our app-based approach did not follow the Tinnitus Retraining Therapy protocol.

Treatment compliance was assessed via participation in CBT treatment sessions (≥6 CBT sessions; including the first two), usage log files for HAs (average use of ≥4 hours/day) and app-use logfiles for SC (completion of the first six chapters) and ST (using each of the four sound stimuli categories once)[17]. Demographic and clinical characteristics were assessed at baseline (before treatment) using the European School of Interdisciplinary Tinnitus Research Screening Questionnaire (ESIT-SQ).[38] Outcome measures were assessed at baseline, interim

(after 6 weeks of treatment), final (after 12-week treatment period), and follow-up (36 weeks after baseline) visits. An additional follow-up visit was conducted 48 weeks after baseline. This visit was a voluntary follow-up visit. Due to a large amount of missing data (only 32.54% of participating patients provided data), no reliable conclusions can be drawn from the analysis and therefore this additional follow-up was not included in the final outcome measure analysis.

Outcome measures

The primary outcome between single and combination treatment was the difference in total score change from baseline to final visit (after 12 weeks of treatment) in the Tinnitus Handicap Inventory (THI).[32] The THI consists of 25 items designed to evaluate the perceived impact of tinnitus on an individual's daily life. Each item provides three response options: "No", "Sometimes" and "Yes", which are scored as 0,2 and 4 points respectively. The total THI score is obtained by summing the scores of all items, resulting in a score that ranges from 0 to 100, with higher sores indicating greater perceived handicap due to tinnitus. Changes from baseline to interim visit, and follow-up were examined in secondary analyses as well. Despite some critique on its sensitivity, [39,40] the THI was chosen as the primary outcome measure, since i) it is the most widely used instrument in clinical settings and is recommended as an outcome for clinical trials based on expert consensus,[41–43] ii) there is high evidence of a conformity between the THI, the Tinnitus Functional Index (TFI)[44], and the Tinnitus Questionnaire (TQ),[45] plus iii) a validated version was available in the required languages (Dutch, German, Greek, Spanish) at the time of trial registration and the definition of our primary outcome measure. [46–49]

Secondary outcome measures included the TFI, the Mini Tinnitus Questionnaire (Mini-TQ),[50] the Patient Health Questionnaire for Depression (PHQ-D/PHQ-9),[51] the abbreviated version of the World Health Organisation - Quality of Life questionnaire (WHO-QoL)[52] as well as numeric rating scales (NRS; 0 - 10) for tinnitus impairment (0 - not a problem; 10 - very big problem), tinnitus loudness (0 - not at all loud; 10 - extremely loud), tinnitus-related discomfort

(0 - no discomfort; 10 - severe discomfort), annoyance (0 - not at all annoying; 10 - extremely annoying), unpleasantness (0 - not at all unpleasant; 10 - extremely unpleasant), and ability to ignore the tinnitus (0 - very easy to ignore; 10 - impossible to ignore).[53] Clinical improvement was measured with the Clinical Global Impression Scale – Improvement (CGI-I).[54] There is expert-based consensus on which outcome domains should be ideally assessed in tinnitus trials. However, there is still no consensus-based recommendation on which standardised instruments should be used within the selected outcome domains.[55] Different secondary outcome measures were considered here to underpin interpretability, validity as well as comparability of potential findings with past and future research.

Questionnaires were filled out by the patients using a graphical interface of the UNITI database.[16] Patients could also opt for paper-pencil versions, and data was subsequently entered into the UNITI database by the local study team.

Adverse (AE) and serious adverse events (SAE) were defined according to the guidelines for Good Clinical Practice §3 (6,8). AEs were assessed and recorded during each visit with respect to start and end date, intensity, relation to intervention, impact on treatment, and actions taken. Any SAE during the 12-week treatment phase led to a stop of the patient's respective treatment and was immediately reported to the local ethics committee.

Statistical Analysis

The sample size was determined a priori on an estimated effect size of 0.26, an alpha level of 5% and a power of 80% (two-sided test). Based on that, the necessary sample size is 468. Considering potential dropouts, the aim was to recruit a total sample size of N = 500.[16]

The statistical analysis was performed in the intention-to-treat (ITT) population of N = 461, including all randomised participants, regardless of compliance with the study protocol. For the primary analysis (combination against single treatments), we estimated that with a two-tailed alpha level of less than 0.05, the sample size of N = 461 provides the trial with 90% power to

detect an effect size of 0.30 (lower end of 95% CI for effect size of behavioural therapy interventions according to the latest Cochrane Review on tinnitus).[25]

For the ITT analysis, missing values (THI: 18%, education: 3.5%, PHQ-9 baseline: 2.6%) were imputed using multilevel imputation (R package `mitml`)[56,57]; see Figure S11 for the distribution of imputed THI values. This approach is considered the gold standard for dealing with missing data.[58] As sensitivity analysis, a per-protocol (PP) was conducted on all patients who met the requirements for treatment compliance as defined in the SAP (N = 185).[17] Additional sensitivity analyses were performed in the primary outcome without imputation, three different reference-based imputation approaches (*jump to reference*, *copy increments in reference*, *copy reference*, R package `RefBasedMI`)[59,60] assuming data is not missing at random and the method of Last Observation Carried Forward. The analysis of the primary objective was performed in the ITT population to test the effectiveness of combination treatments against single treatments (control group). Further comparisons between single versus combination treatments for all 4 single treatments separately (CBT single vs. combined, HA single vs. combined, SC single vs. combined, ST single vs. combined) as well as comparisons between all ten treatment arms were performed. Detailed information on which treatment arms were pooled for which type of comparison can be found in the SAP.[17]

To address all objectives, mixed effect models were applied (with REML using the `lme4` R package)[61] by considering the outcome as the response variable and including the corresponding objective, time point (baseline, interim visit, final visit, and follow-up), and objective-by-time interaction as fixed effects, including centre and subject ID as random intercepts. The models were adjusted for the following covariates: age, sex, educational attainment, hearing aid indication, and PHQ-9 baseline scores.[17] The results of the remaining objectives as described in the SAP are reported in the Supplementary Appendix. Additionally, we evaluated THI score changes from baseline to final visit for single and combination treatment as well as all individual treatment arms separately by country to assess potential country-specific effects.

Results are reported as least-squares mean changes (obtained via the `emmeans` R package)[62] with 95% CI. All analyses were performed in R (version 4.2.2).

De-identified data (pseudo-anonymised code) were gathered in a central database, which was regularly monitored and systematically checked for missing and invalid data (every six weeks). After database closure and prior to analysis, data from each clinical centre were checked again for validity and completeness. This study was registered at ClinicalTrials.gov, NCT04663828.

Data availability

De-identified data reported and analysed here will be available upon request to the corresponding author. The complete dataset (incl. 48-week follow-up) and its description is currently under preparation for publication and release via ZENODO. Status of the data availability will be updated on the UNITI website (https://uniti.tinnitusresearch.net/).

References

1. De Ridder, D. *et al.* Tinnitus and tinnitus disorder: Theoretical and operational definitions (an international multidisciplinary proposal). *Prog. Brain Res.* **260**, 1–25 (2021).
2. Jarach, C. M. *et al.* Global Prevalence and Incidence of Tinnitus: A Systematic Review and Meta-analysis. *JAMA Neurol.* **79**, 888–900 (2022).
3. Baguley, D., McFerran, D. & Hall, D. Tinnitus. *The Lancet* **382**, 1600–1607 (2013).
4. Roberts, L. E. *et al.* Ringing Ears: The Neuroscience of Tinnitus. *J. Neurosci.* **30**, 14972–14979 (2010).
5. Vanneste, S. & De Ridder, D. The auditory and non-auditory brain areas involved in tinnitus. An emergent property of multiple parallel overlapping subnetworks. *Front. Syst. Neurosci.* **6**, 31 (2012).
6. Sanchez, T. G., Valim, C. C. A. & Schlee, W. Long-lasting total remission of tinnitus: A systematic collection of cases. *Prog. Brain Res.* **260**, 269–282 (2021).
7. Mazurek, B. *et al.* S3 Guideline: Chronic Tinnitus: German Society for Otorhinolaryngology, Head and Neck Surgery e. V. (DGHNO-KHC). *HNO* **70**, 795–827 (2022).
8. Cima, R. F. F. *et al.* A multidisciplinary European guideline for tinnitus: diagnostics, assessment, and treatment. *HNO* (2019) doi:10.1007/s00106-019-0633-7.
9. Bauer, C. A., Berry, J. L. & Brozoski, T. J. The effect of tinnitus retraining therapy on chronic tinnitus: A controlled trial: A Controlled Trial of Tinnitus Retraining Therapy. *Laryngoscope Investig. Otolaryngol.* **2**, 166–177 (2017).
10. Cima, R. F. *et al.* Specialised treatment based on cognitive behaviour therapy versus usual care for tinnitus: a randomised controlled trial. *The Lancet* **379**, 1951–1959 (2012).
11. Henry, J. A. *et al.* Tinnitus Management: Randomized Controlled Trial Comparing

523 Extended-Wear Hearing Aids, Conventional Hearing Aids, and Combination Instruments. *J.*
524 *Am. Acad. Audiol.* **28**, 546–561 (2017).
525 12. Tyler, R. S., Gogel, S. A. & Gehringer, A. K. Tinnitus activities treatment. *Prog.*
526 *Brain Res.* **166**, 425–434 (2007).
527 13. Jastreboff, P. J. 25 Years of tinnitus retraining therapy. *HNO* **63**, 307–311 (2015).
528 14. Tunkel, D. E. *et al.* Clinical practice guideline: tinnitus executive summary.
529 *Otolaryngol.--Head Neck Surg. Off. J. Am. Acad. Otolaryngol.-Head Neck Surg.* **151**, 533–
530 541 (2014).
531 15. Kikidis, D. *et al.* Methodological Aspects of Randomized Controlled Trials for
532 Tinnitus: A Systematic Review and How a Decision Support System Could Overcome
533 Barriers. *J. Clin. Med.* **10**, 1737 (2021).
534 16. Schoisswohl, S. *et al.* Unification of Treatments and Interventions for Tinnitus
535 Patients (UNITI): a study protocol for a multi-center randomized clinical trial. *Trials* **22**, 875
536 (2021).
537 17. Simoes, J. P. *et al.* The statistical analysis plan for the unification of treatments and
538 interventions for tinnitus patients randomized clinical trial (UNITI-RCT). *Trials* **24**, 472
539 (2023).
540 18. Searchfield, G. D. & Sanders, P. J. A randomized single-blind controlled trial of a
541 prototype digital polytherapeutic for tinnitus. *Front. Neurol.* **13**, (2022).
542 19. Conlon, B. *et al.* Different bimodal neuromodulation settings reduce tinnitus
543 symptoms in a large randomized trial. *Sci. Rep.* **12**, 10845 (2022).
544 20. Langguth, B., Kleinjung, T., Schlee, W., Vanneste, S. & De Ridder, D. Tinnitus
545 Guidelines and Their Evidence Base. *J. Clin. Med.* **12**, 3087 (2023).
546 21. Sereda, M., Xia, J., El Refaie, A., Hall, D. A. & Hoare, D. J. Sound therapy (using
547 amplification devices and/or sound generators) for tinnitus. *Cochrane Database Syst. Rev.* **12**,
548 CD013094 (2018).
549 22. Kikidis, D., Vassou, E., Markatos, N., Schlee, W. & Iliadou, E. Hearing Aid Fitting in
550 Tinnitus: A Scoping Review of Methodological Aspects and Effect on Tinnitus Distress and
551 Perception. *J. Clin. Med.* **10**, 2896 (2021).
552 23. Henry, J. A., Carlson, K. F., Theodoroff, S. & Folmer, R. L. Reevaluating the Use of
553 Sound Therapy for Tinnitus Management: Perspectives on Relevant Systematic Reviews. *J.*
554 *Speech Lang. Hear. Res. JSLHR* **65**, 2327–2342 (2022).
555 24. Schlee, W. *et al.* Smartphone-Guided Educational Counseling and Self-Help for
556 Chronic Tinnitus. *J. Clin. Med.* **11**, 1825 (2022).
557 25. Fuller, T. *et al.* Cognitive behavioural therapy for tinnitus. *Cochrane Database Syst.*
558 *Rev.* **1**, CD012614 (2020).
559 26. Schecklmann, M., Weber, F. C., Lehner, A., Langguth, B. & Schoisswohl, S.
560 Cognitive Behavioral Group Therapy for Chronic Tinnitus in a German Tertiary Clinical
561 Real-World Setting. *Int. J. Environ. Res. Public. Health* **20**, 4982 (2023).
562 27. Schiele, T. *et al.* Predictors of Tinnitus Symptom Relief With Hearing Aids in a
563 European Multicenter Study. *Ear Hear.* (2025).
564 28. Gninenko, N. *et al.* Functional MRI Neurofeedback Outperforms Cognitive
565 Behavioral Therapy for Reducing Tinnitus Distress: A Prospective Randomized Clinical
566 Trial. *Radiology* **310**, e231143 (2024).
567 29. Meyerowitz-Katz, G. *et al.* Rates of Attrition and Dropout in App-Based Interventions
568 for Chronic Disease: Systematic Review and Meta-Analysis. *J. Med. Internet Res.* **22**, e20283
569 (2020).
570 30. Schlee, W. *et al.* Towards a unification of treatments and interventions for tinnitus
571 patients: The EU research and innovation action UNITI. *Prog. Brain Res.* **260**, 441–451
572 (2021).
573 31. Schulz, K. F., Altman, D. G. & Moher, D. CONSORT 2010 statement: Updated

574 guidelines for reporting parallel group randomised trials. *J. Pharmacol. Pharmacother.* **1**,
575 100–107 (2010).
576 32. Newman, C. W., Jacobson, G. P. & Spitzer, J. B. Development of the Tinnitus
577 Handicap Inventory. *Arch. Otolaryngol. Head Neck Surg.* **122**, 143–148 (1996).
578 33. Nasreddine, Z. S. *et al.* The Montreal Cognitive Assessment, MoCA: a brief screening
579 tool for mild cognitive impairment. *J. Am. Geriatr. Soc.* **53**, 695–699 (2005).
580 34. Cima, R. F. F. Bothersome tinnitus : Cognitive behavioral perspectives. *HNO* **66**, 369–
581 374 (2018).
582 35. Cima, R. F. F., van Breukelen, G. & Vlaeyen, J. W. S. Tinnitus-related fear: Mediating
583 the effects of a cognitive behavioural specialised tinnitus treatment. *Hear. Res.* **358**, 86–97
584 (2018).
585 36. Keidser, G., Dillon, H., Flax, M., Ching, T. & Brewer, S. The NAL-NL2 Prescription
586 Procedure. *Audiol. Res.* **1**, (2011).
587 37. Vogel, C., Schobel, J., Schlee, W., Engelke, M. & Pryss, R. UNITI Mobile-EMI-Apps
588 for a Large-Scale European Study on Tinnitus. *Annu. Int. Conf. IEEE Eng. Med. Biol. Soc.*
589 *IEEE Eng. Med. Biol. Soc. Annu. Int. Conf.* **2021**, 2358–2362 (2021).
590 38. Genitsaridi, E. *et al.* Standardised profiling for tinnitus research: The European School
591 for Interdisciplinary Tinnitus Research Screening Questionnaire (ESIT-SQ). *Hear. Res.* **377**,
592 353–359 (2019).
593 39. Tyler, R. S., Noble, W. & Coelho, C. Considerations for the design of clinical trials for
594 tinnitus. *Acta Otolaryngol. (Stockh.)* **126**, 44–49 (2006).
595 40. Tyler, R. S., Oleson, J., Noble, W., Coelho, C. & Ji, H. Clinical trials for tinnitus:
596 study populations, designs, measurement variables, and data analysis. in *Progress in Brain*
597 *Research* (eds. Langguth, B., Hajak, G., Kleinjung, T., Cacace, A. & Møller, A. R.) vol. 166
598 499–509 (Elsevier, 2007).
599 41. Hall, D. A. *et al.* Systematic review of outcome domains and instruments used in
600 clinical trials of tinnitus treatments in adults. *Trials* **17**, 270 (2016).
601 42. Fuller, T. E. *et al.* Different Teams, Same Conclusions? A Systematic Review of
602 Existing Clinical Guidelines for the Assessment and Treatment of Tinnitus in Adults. *Front.*
603 *Psychol.* **8**, 206 (2017).
604 43. Langguth, B. *et al.* Consensus for tinnitus patient assessment and treatment outcome
605 measurement: Tinnitus Research Initiative meeting, Regensburg, July 2006. *Prog. Brain Res.*
606 **166**, 525–536 (2007).
607 44. Meikle, M. *et al.* The Tinnitus Functional Index: Development of a New Clinical
608 Measure for Chronic, Intrusive Tinnitus. *Ear Hear.* **33**, 153–76 (2011).
609 45. Boecking, B., Brueggemann, P., Kleinjung, T. & Mazurek, B. All for One and One for
610 All? – Examining Convergent Validity and Responsiveness of the German Versions of the
611 Tinnitus Questionnaire (TQ), Tinnitus Handicap Inventory (THI), and Tinnitus Functional
612 Index (TFI). *Front. Psychol.* **12**, 630 (2021).
613 46. Papitsi, I. *et al.* Validation of the Greek Version of Tinnitus Handicap Inventory.
614 *Audiol. Res.* **10**, 39–48 (2020).
615 47. Kleinjung, T. *et al.* Validierung einer deutschsprachigen Version des „Tinnitus
616 Handicap Inventory". *Psychiatr. Prax.* **34**, S140–S142 (2007).
617 48. Herráiz, C., Hernández calvín, J., Plaza, G., Tapia, M. C. & De los santos, G.
618 Evaluación de la incapacidad en pacientes con acúfenos. *Acta Otorrinolaringológica Esp.* **52**,
619 534–538 (2001).
620 49. Brussee, L. Tinnitus 'een permanente stoorzender'. *Tinnitus Een Perm. Stoorzender*
621 (2003).
622 50. Hiller, W. & Goebel, G. Rapid assessment of tinnitus-related psychological distress
623 using the Mini-TQ. *Int. J. Audiol.* **43**, 600–604 (2004).
624 51. Kroenke, K. & Spitzer, R. L. The PHQ-9: A New Depression Diagnostic and Severity

Measure. *Psychiatr. Ann.* **32**, 509–515 (2002).
52. Harper, A., Power, M. & WHOQOL Group, X. Development of the World Health Organization WHOQOL-Bref quality of life assessment. *Psychol. Med.* 551–558 (1998).
53. Landgrebe, M. *et al.* The Tinnitus Research Initiative (TRI) database: A new approach for delineation of tinnitus subtypes and generation of predictors for treatment outcome. *BMC Med. Inform. Decis. Mak.* **10**, (2010).
54. Adamchic, I. *et al.* Linking the Tinnitus Questionnaire and the subjective Clinical Global Impression: Which differences are clinically important? *Health Qual. Life Outcomes* **10**, 79 (2012).
55. Hall, D. A. *et al.* The COMiT'ID Study: Developing Core Outcome Domains Sets for Clinical Trials of Sound-, Psychology-, and Pharmacology-Based Interventions for Chronic Subjective Tinnitus in Adults. *Trends Hear.* **22**, 2331216518814384 (2018).
56. Quartagno, M., Grund, S. & Carpenter, J. jomo: A Flexible Package for Two-level Joint Modelling Multiple Imputation. *R J.* **11**, 205–228 (2019).
57. Grund, S., Robitzsch, A. & Luedtke, O. mitml: Tools for Multiple Imputation in Multilevel Modeling. (2023).
58. Pedersen, A. B. *et al.* Missing data and multiple imputation in clinical epidemiological research. *Clin. Epidemiol.* **9**, 157–166 (2017).
59. Cro, S., Morris, T. P., Kenward, M. G. & Carpenter, J. R. Reference-based Sensitivity Analysis via Multiple Imputation for Longitudinal Trials with Protocol Deviation. *Stata J.* **16**, 443–463 (2016).
60. McGrath, K. & Quartagno, M. RefBasedMI: Reference-Based Imputation for Longitudinal Clinical Trials with Protocol Deviation. (2024).
61. Bates, D., Mächler, M., Bolker, B. & Walker, S. Fitting Linear Mixed-Effects Models Using **lme4**. *J. Stat. Softw.* **67**, (2015).
62. Lenth, R. V. *et al.* emmeans: Estimated Marginal Means, aka Least-Squares Means. (2023).

Author Contributions

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All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. SSch, WS, LB, and ME have directly accessed and verified the underlying data reported in the manuscript.

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Competing interests

The authors declare no competing interests.

Tables

Table 1. Demographic and clinical characteristics of the participants at baseline (stratified by treatment arm).											
Characteristics	**CBT (n=56)**	**HA (n=59)**	**SC (n=56)**	**ST (n=59)**	**CBT+HA (n=17)**	**CBT+SC (n=51)**	**CBT+ST (n=54)**	**HA+SC (n=19)**	**HA+ST (n=27)**	**SC+ST (n=63)**	**Overall (N=461)**
Demographic characteristics											
Sex											
Male (%)	34 (60.7%)	36 (61.0%)	39 (69.6%)	32 (54.2%)	12 (70.6%)	27 (52.9%)	33 (61.1%)	12 (63.2%)	18 (66.7%)	28 (44.4%)	271 (58.8%)
Female (%)	22 (39.3%)	23 (39.0%)	17 (30.4%)	27 (45.8%)	5 (29.4%)	24 (47.1%)	21 (38.9%)	7 (36.8%)	9 (33.3%)	35 (55.6%)	190 (41.2%)
Age (years)	48.8 ±12.3	53.4 ±11.7	49.8 ±13.1	50.3 ±14.0	56.0 ±10.4	54.0 ±12.0	46.4 ±12.9	51.6 ±14.0	55.0 ±11.2	51.2 ±9.8	51.1 ±12.4
PHQ-9 total score	7.3 ±4.9	7.3 ±4.8	7.2 ±4.5	8.5 ±5.2	5.8 ±4.6	6.8 ±4.3	7.9 ±5.0	6.8 ±3.2	7.0 ±5.6	7.0 ±5.5	7.3 ±4.9
Tinnitus characteristics											
Tinnitus duration (in months)	119 ±127	126 ±100	85 ±77	115 ±114	101 ±111	154 ±140	110 ±99	159 ±144	124 ±108	119 ±116	119 ±113
Hearing aid indication (%)	19 (33.9%)	59 (100%)	19 (33.9%)	20 (33.9%)	17 (100%)	18 (35.3%)	17 (31.5%)	19 (100%)	27 (100%)	19 (30.2%)	234 (50.8%)
THI total score	47.8 ±20.3	48.8 ±19.2	48.6 ±20.6	48.7 ±18.1	42.2 ±18.9	45.5 ±18.9	48.0 ±19.3	52.2 ±21.9	50.1 ±20.1	47.2 ±20.9	48.0 ±19.7
TFI total score	47.8 ±21.4	50.6 ±18.8	48.5 ±20.7	50.9 ±18.1	46.1 ±18.9	42.9 ±18.8	47.4 ±22.7	51.7 ±21.3	54.5 ±21.4	48.1 ±20.9	48.6 ±20.3
Mini-TQ total score	11.4 ±5.2	12.2 ±4.6	11.8 ±5.4	12.5 ±5.0	10.7 ±4.0	11.2 ±5.0	12.3 ±4.6	11.9 ±5.2	12.3 ±6.0	12.0 ±5.2	11.9 ±5.0
Tinnitus loudness (rating)	6.2 ±2.1	6.7 ±1.7	6.4 ±2.4	6.3 ±2.1	6.3 ±2.7	6.0 ±2.6	6.2 ±2.6	6.4 ±2.3	7.2 ±1.6	6.3 ±2.2	6.4 ±2.2

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.

Data are n (%) or mean ± SD. PHQ-9 scores range from 0 to 27, with higher scores indicating greater severity of depression. The definition for hearing aid indication is given in Table S3. THI scores range from 0 to 100, with higher scores indicating greater severity of tinnitus. TFI scores range from 0 to 100, with higher scores indicating greater severity of tinnitus. Mini-TQ scores range from 0 to 24, with higher scores indicating greater severity of tinnitus. Tinnitus loudness (rating) scores range from 0 to 10, with higher scores indicating greater loudness of tinnitus. Abbreviations: CBT = Cognitive-Behavioural Therapy; HA = Hearing Aids; PHQ-9 = Patient Health Questionnaire for Depression; SC = Structured Counselling; ST = Sound Therapy; TFI = Tinnitus Functional Index; THI = Tinnitus Handicap Inventory; TQ = Tinnitus Questionnaire

.

Table 2. Primary and Secondary Clinical Outcomes at Final Visit: Single vs. Combination (Intention-to-Treat Population).										
	All treatments		**Cognitive Behavioural Therapy**		**Hearing Aid**		**Structured Counselling**		**Sound Therapy**	
	Single	Combination	Single	Combination	Single	Combination	Single	Combination	Single	Combination
Primary outcome										
THI										
Change from baseline	-11.7	-14.9	-16.9	-15.6	-14.4	-15.7	-12.0	-15.5	-3.8	-13.2
(95% CI)	(-14.4 to -9.0)	(-17.7 to -12.1)	(-22.8 to -10.9)	(-19.5 to -11.7)	(-19.5 to -9.4)	(-20.7 to -10.7)	(-17.5 to -6.5)	(-19.3 to -11.7)	(-9.3 to 1.6)	(-16.7 to -9.8)
Secondary Outcome										
TFI										
Change from baseline	-11.0	-11.6	-16.1	-12.1	-14.5	-13.9	-9.7	-10.1	-3.7	-11.7
(95% CI)	(-13.9 to -8.0)	(-14.7 to -8.5)	(-22.1 to -10.1)	(-16.3 to -7.9)	(-20.2 to -8.9)	(-19.4 to -8.4)	(-15.5 to -3.9)	(-14.0 to -6.2)	(-9.6 to 2.1)	(-15.5 to -7.9)
Mini-TQ										
Change from baseline	-2.9	-3.4	-4.1	-3.8	-3.5	-3.0	-2.9	-3.4	-1.2	-3.0
(95% CI)	(-3.6 to -2.2)	(-4.1 to -2.7)	(-5.5 to -2.6)	(-4.8 to -2.8)	(-4.7 to -2.4)	(-4.2 to -1.9)	(-4.3 to -1.4)	(-4.3 to -2.5)	(-2.6 to 0.2)	(-3.9 to -2.2)
NRS - tinnitus loudness										
Change from baseline	-0.8	-0.8	-0.5	-0.8	-1.4	-0.8	-0.8	-0.7	-0.3	-0.8
(95% CI)	(-1.2 to -0.4)	(-1.2 to -0.4)	(-1.4 to 0.3)	(-1.4 to -0.2)	(-2.2 to -0.6)	(-1.6 to -0.1)	(-1.6 to 0.0)	(-1.2 to -0.2)	(-1.0 to 0.5)	(-1.3 to -0.3)
PHQ-9										
Change from baseline	-1.7	-1.4	-1.7	-1.7	-2.3	-1.5	-1.7	-1.3	-0.8	-1.3
(95% CI)	(-2.3 to -1.0)	(-2.1 to -0.8)	(-3.0 to -0.3)	(-2.6 to -0.8)	(-3.5 to -1.2)	(-2.6 to -0.4)	(-3.1 to -0.4)	(-2.2 to -0.5)	(-2.2 to 0.6)	(-2.2 to -0.4)

721 **Table 2. Primary and Secondary Clinical Outcomes at Final Visit: Single vs. Combination (ITT).**

Values depict least-squares mean changes at week 12 for primary and secondary outcomes with 95% confidence intervals. Higher total scores on the THI, TFI and Mini-TQ indicate greater severity of tinnitus. Higher total scores on the NRS - tinnitus loudness indicate greater loudness of tinnitus. Higher total scores on the PHQ-9 indicate greater severity of depression. Further objectives and secondary clinical outcomes not reported in this table can be seen in the Supplementary Appendix. Abbreviations: NRS = Numeric Rating Scale; PHQ-9 = Patient Health Questionnaire for Depression; TFI = Tinnitus Functional Index; THI = Tinnitus Handicap Inventory; TQ = Tinnitus Questionnaire.

Table 3. Primary and Secondary Clinical Outcomes at Final Visit: All Treatment Arms (Intention-to-Treat Population).										
	CBT	**HA**	**SC**	**ST**	**CBT+HA**	**CBT+SC**	**CBT+ST**	**HA+SC**	**HA+ST**	**SC+ST**
Primary outcome										
THI										
Change from baseline	-16.9	-14.4	-12.0	-3.8	-15.2	-17.4	-14.1	-20.0	-12.9	-12.7
(95% CI)	(-22.7 to -11.0)	(-19.7 to -9.2)	(-17.5 to -6.5)	(-9.2 to 1.5)	(-26.0 to -4.4)	(-23.8 to -11.0)	(-19.8 to -8.4)	(-29.3 to -10.8)	(-20.5 to -5.3)	(-17.8 to -7.5)
Cohen's d (95% CI)	0.93 (0.70 to 1.21)	1.00 (0.78 to 1.28)	0.83 (0.51 to 1.27)	0.24 (-0.02 to 0.53)	1.13 (0.74 to 1.83)	1.19 (0.91 to 1.59)	0.80 (0.55 to 1.12)	1.35 (0.98 to 1.99)	0.78 (0.43 to 1.37)	0.71 (0.46 to 1.02)
Secondary Outcome										
TFI										
Change from baseline	-16.1	-14.5	-9.7	-3.7	-15.1	-10.9	-12.2	-10.1	-15.8	-9.4
(95% CI)	(-22.2 to -10.0)	(-20.1 to -8.9)	(-15.6 to -3.8)	(-9.5 to 2.0)	(-26.1 to -4.0)	(-17.4 to -4.4)	(-18.5 to -5.9)	(-20.0 to -0.2)	(-24.0 to -7.6)	(-15.1 to -3.8)
Mini-TQ										
Change from baseline	-4.1	-3.5	-2.9	-1.2	-4.0	-4.1	-3.6	-3.2	-2.3	-2.9
(95% CI)	(-5.5 to -2.6)	(-4.8 to -2.2)	(-4.3 to -1.4)	(-2.6 to 0.2)	(-6.7 to -1.3)	(-5.6 to -2.6)	(-5.0 to -2.2)	(-5.5 to -0.9)	(-4.3 to -0.4)	(-4.2 to -1.6)
NRS - tinnitus loudness										
Change from baseline	-0.5	-1.4	-0.8	-0.3	-1.0	-0.9	-0.7	-0.3	-1.1	-0.7
(95% CI)	(-1.4 to 0.3)	(-2.1 to -0.6)	(-1.6 to 0.0)	(-1.1 to 0.5)	(-2.5 to 0.6)	(-1.8 to 0.0)	(-1.5 to 0.1)	(-1.6 to 1.1)	(-2.2 to -0.1)	(-1.5 to 0.0)
PHQ-9										
Change from baseline	-1.7	-2.3	-1.7	-0.9	-1.2	-1.8	-1.8	-2.0	-1.3	-0.8
(95% CI)	(-3.0 to -0.3)	(-3.6 to -1.1)	(-3.1 to -0.4)	(-2.2 to 0.4)	(-3.7 to 1.2)	(-3.2 to -0.3)	(-3.2 to -0.4)	(-4.2 to 0.2)	(-3.1 to 0.6)	(-2.1 to 0.4)

Table 3. Primary and Secondary Clinical Outcomes at Final Visit: All treatment Arms (ITT).
Values depict least-squares mean changes at week 12 for primary and secondary outcomes with 95% confidence intervals. Higher total scores on the THI, TFI and Mini-TQ indicate greater severity of tinnitus. Higher total scores on the NRS - tinnitus loudness indicate greater loudness of tinnitus. Higher total scores on the PHQ-9 indicate greater severity of depression. Cohens d indicate the standardised effect size of the respective treatment. The effect sizes and the corresponding confidence intervals were first computed in each of the 50 imputed data sets before they were averaged to a single value. Further objectives and secondary clinical outcomes not reported in this table can be seen in the Supplementary

Appendix. Abbreviations: CBT = Cognitive-Behavioural Therapy; HA = Hearing Aids; NRS = Numeric Rating Scale; PHQ-9 = Patient Health Questionnaire for Depression; SC = Structured Counselling; ST = Sound Therapy; TFI = Tinnitus Functional Index; THI = Tinnitus Handicap Inventory; TQ = Tinnitus Questionnaire.

Figure legends

Figure 1. Trial Profile. A total of 674 patients were screened, of whom 461 met the trial inclusion criteria and were randomly assigned to one of ten treatment arms comprised of a single treatment or a combination of two treatments out of four different therapy approaches - cognitive-behavioural therapy (CBT), hearing aids (HA), structured counselling (SC), and sound therapy (ST). 230 (49.9%) were assigned to single treatments (CBT, HA, SC, or ST) and 231 (50.1%) were assigned to combination treatments (CBT+HA, CBT+SC, CBT+ST, HA+SC, HA+ST, SC+ST). Patients without hearing aid indication were only randomised to treatments without HA. An extended version of the patient's flowchart can be found in Figure S1. Quantity and reasons for trial exclusion during eligibility assessments and trial discontinuation/dropouts can be seen from Tables S1 – S5.

Figure 2. Least-Squares Mean Changes from Baseline to interim visit (6w), final visit (12w) and follow-up (36w) in THI total score. A) single (n = 230) and combination (n = 231) treatments; **C)** CBT+HA (n = 17); **D)** CBT+SC (n = 51); **E)** CBT+ST (n = 54); **F)** HA+SC (n = 19); **G)** HA+ST (n = 27); **H)** SC+ST (n = 63); and **B)** Cohen's d values for all treatment arms (change in THI total score from baseline to final visit). Single treatment arms included: CBT (n = 56), HA (n = 59), SC (n = 56) and ST (n = 59). Total THI scores range from 0 to 100, with higher scores indicating greater severity of tinnitus. Error bars represent 95% confidence intervals. Abbreviations: CBT = Cognitive-Behavioural Therapy; HA = Hearing Aids; SC = Structured Counselling; ST = Sound Therapy; THI = Tinnitus Handicap Inventory.

674 participants were assessed for eligibility

213 were excluded
99 did not meet eligibility criteria
107 stratification group completed
6 personal reasons/ declined to participate
1 artificial eardrum

461 underwent randomisation

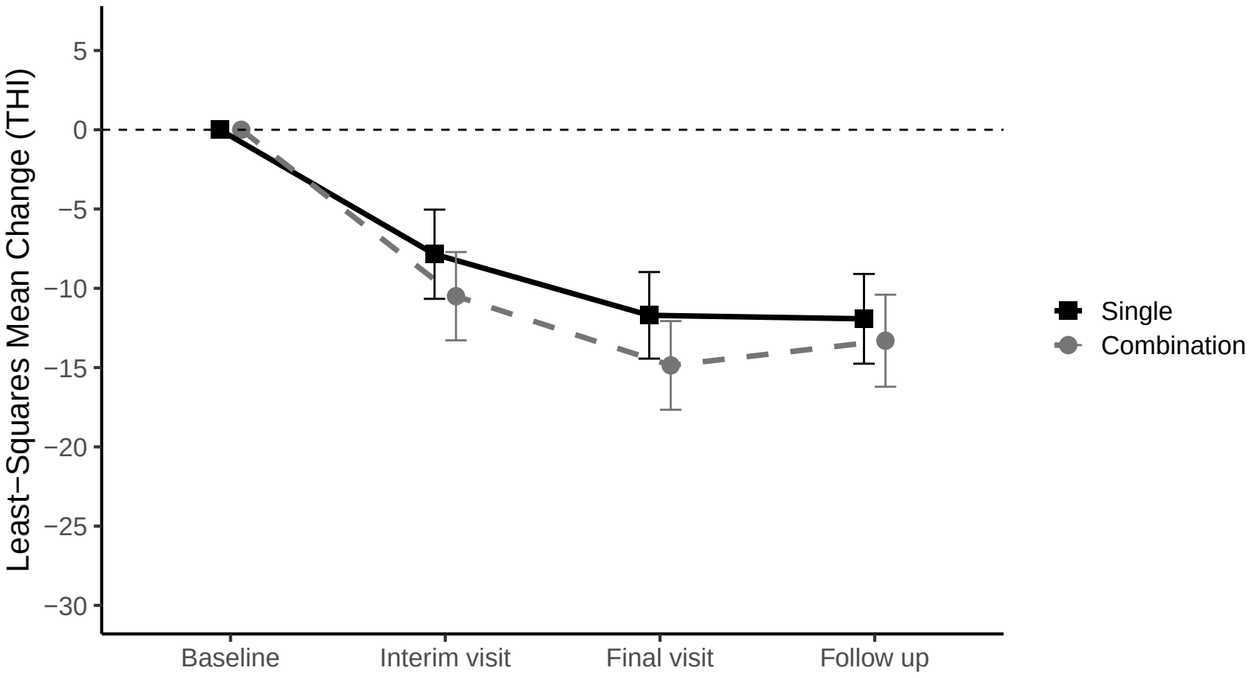
230 single treatment

231 combination treatment

56 CBT	**59 HA**	**56 SC**	**59 ST**	**17 CBT + HA**	**51 CBT + SC**	**54 CBT + ST**	**19 HA + SC**	**27 HA + ST**	**63 SC + ST**
47 treatment starts	58 treatment starts	52 treatment starts	58 treatment starts	12 treatment starts	40 treatment starts	45 treatment starts	18 treatment starts	26 treatment starts	59 treatment starts
43 interim visits	57 interim visits	50 interim visits	56 interim visits	12 interim visits	34 interim visits	39 interim visits	18 interim visits	25 interim visits	56 interim visits
39 treatment completed	54 treatment completed	45 treatment completed	52 treatment completed	11 treatment completed	32 treatment completed	35 treatment completed	18 treatment completed	25 treatment completed	53 treatment completed
34 completed 36-wk follow-up	41 completed 36-wk follow-up	29 completed 36-wk follow-up	45 completed 36-wk follow-up	9 completed 36-wk follow-up	28 completed 36-wk follow-up	30 completed 36-wk follow-up	15 completed 36-wk follow-up	19 completed 36-wk follow-up	47 completed 36-wk follow-up
56 were included in primary analysis	**59 were included in primary analysis**	**56 were included in primary analysis**	**59 were included in primary analysis**	**17 were included in primary analysis**	**51 were included in primary analysis**	**54 were included in primary analysis**	**19 were included in primary analysis**	**27 were included in primary analysis**	**63 were included in primary analysis**

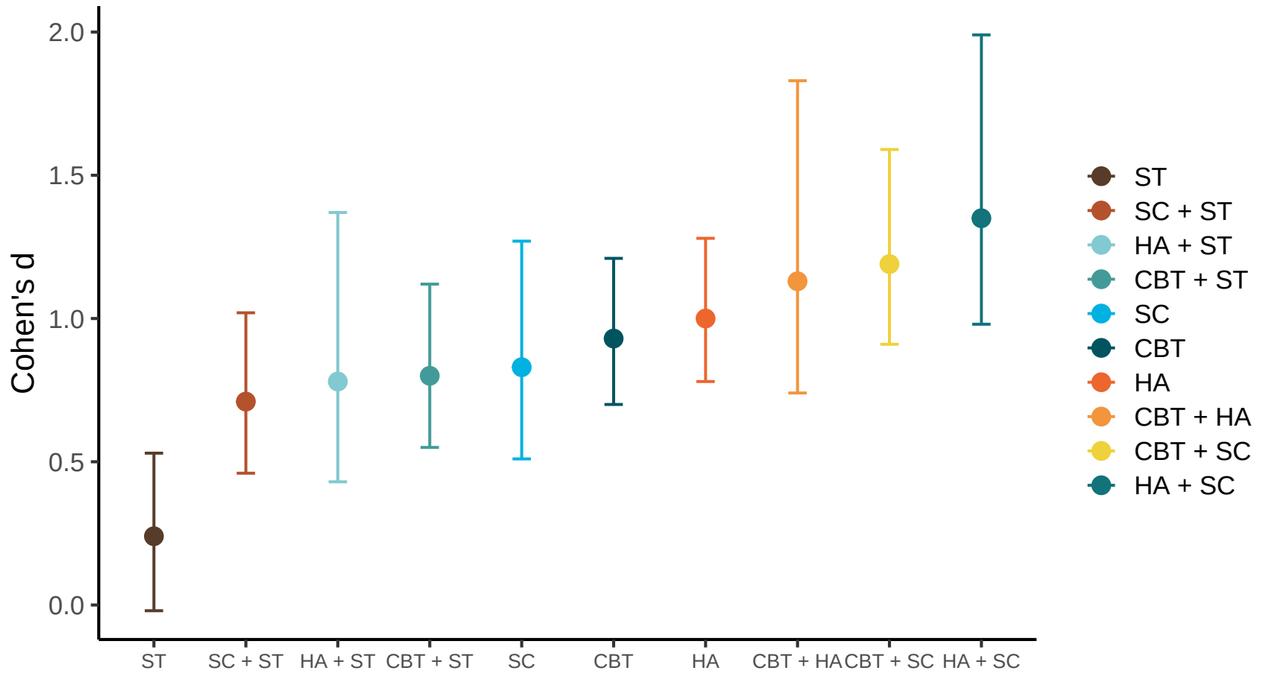
A)

Single vs. Combination Treatments



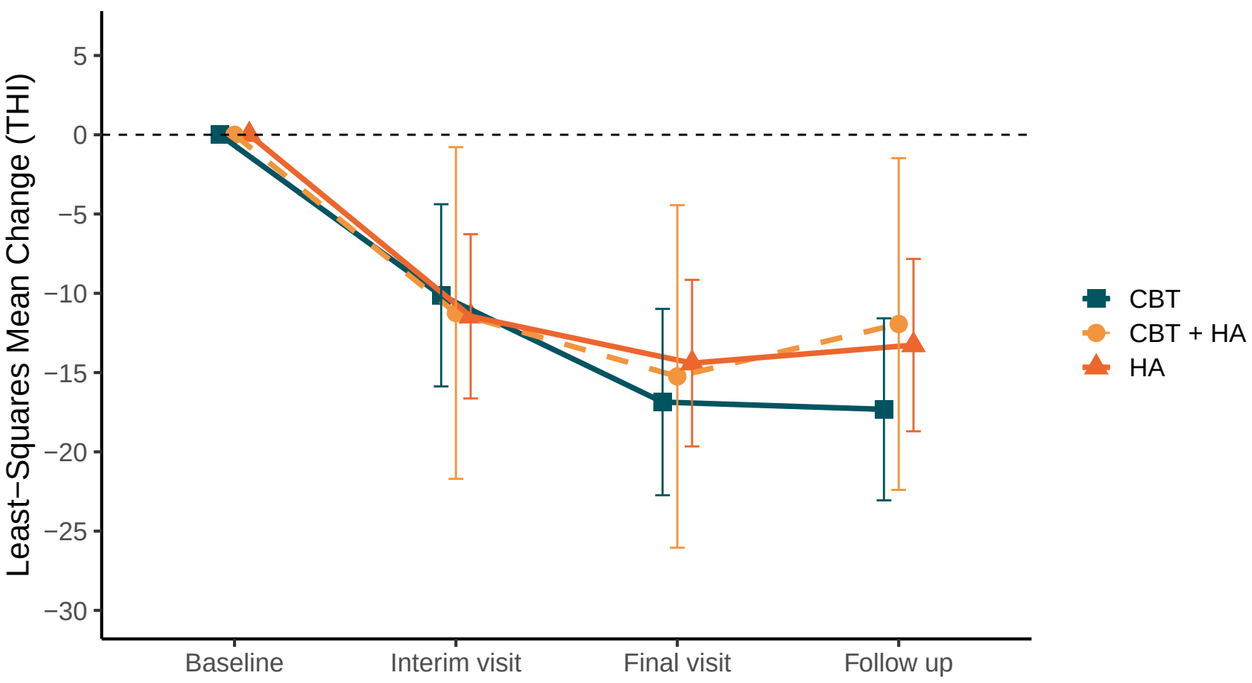
B)

Effect size: THI Change from Baseline to Final Visit



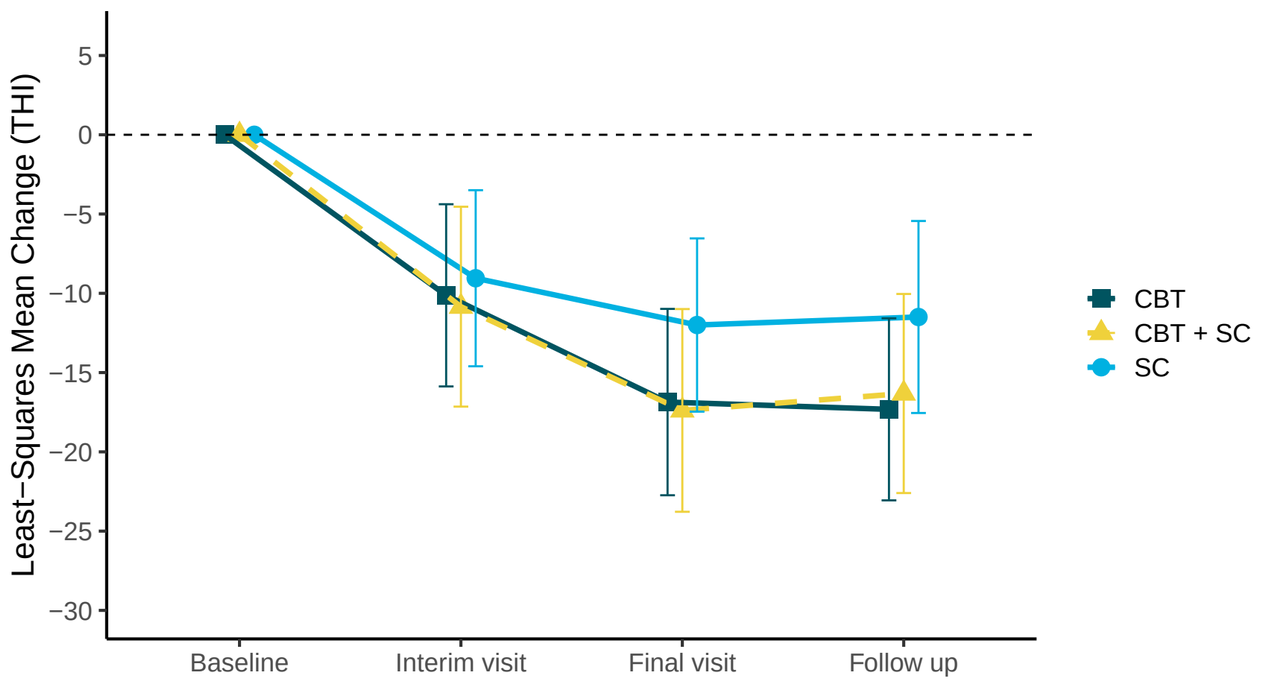
C)

Cognitive Behavioural Therapy + Hearing Aid



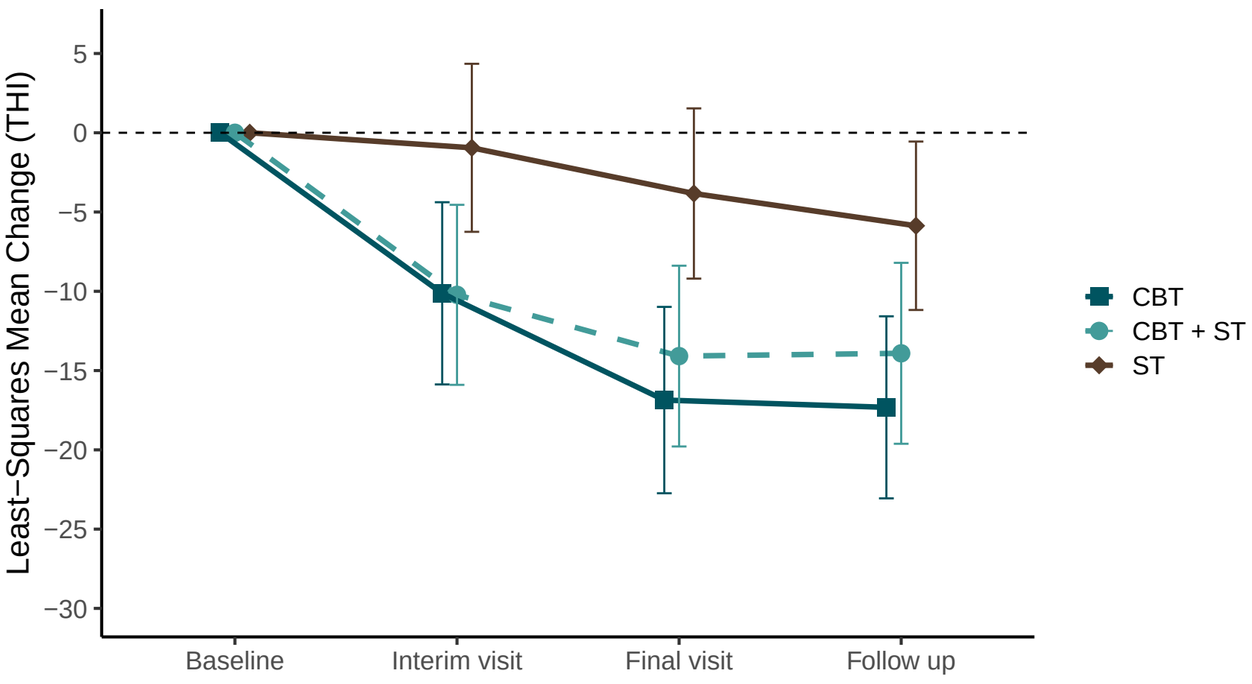
D)

Cognitive Behavioural Therapy + Structured Counselling



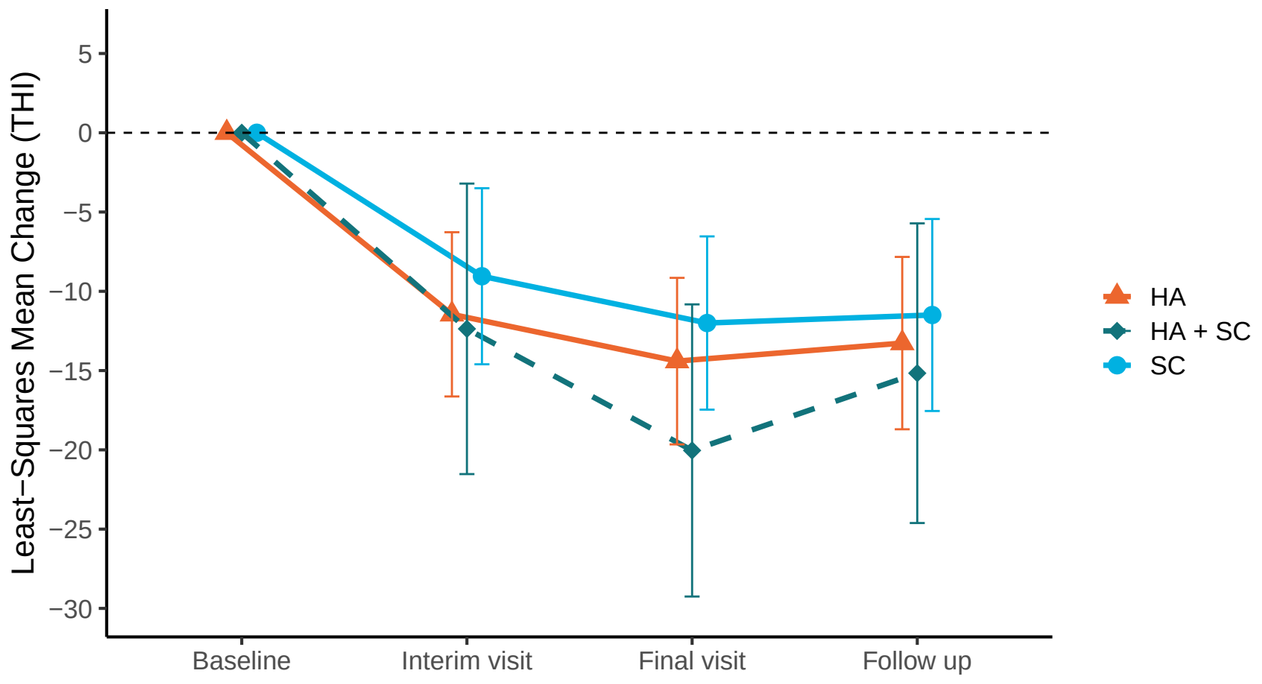
E)

Cognitive Behavioural Therapy + Sound Therapy



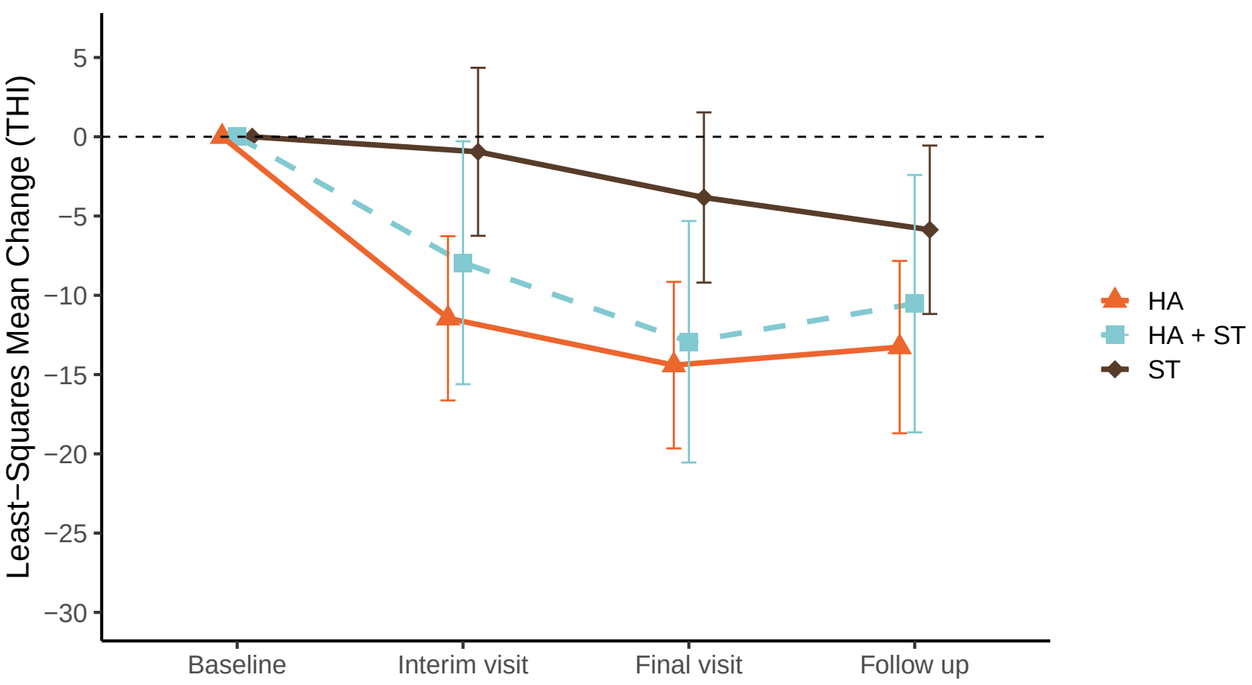
F)

Hearing Aid + Structured Counselling



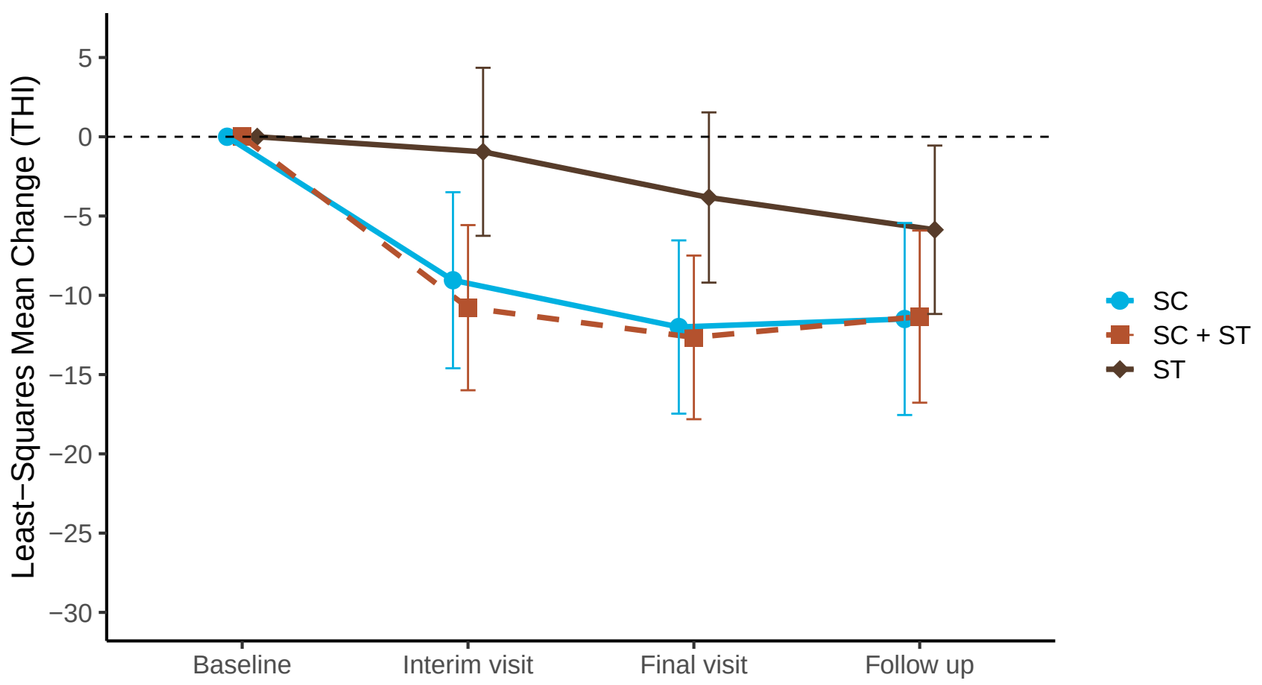
G)

Hearing Aid + Sound Therapy



H)

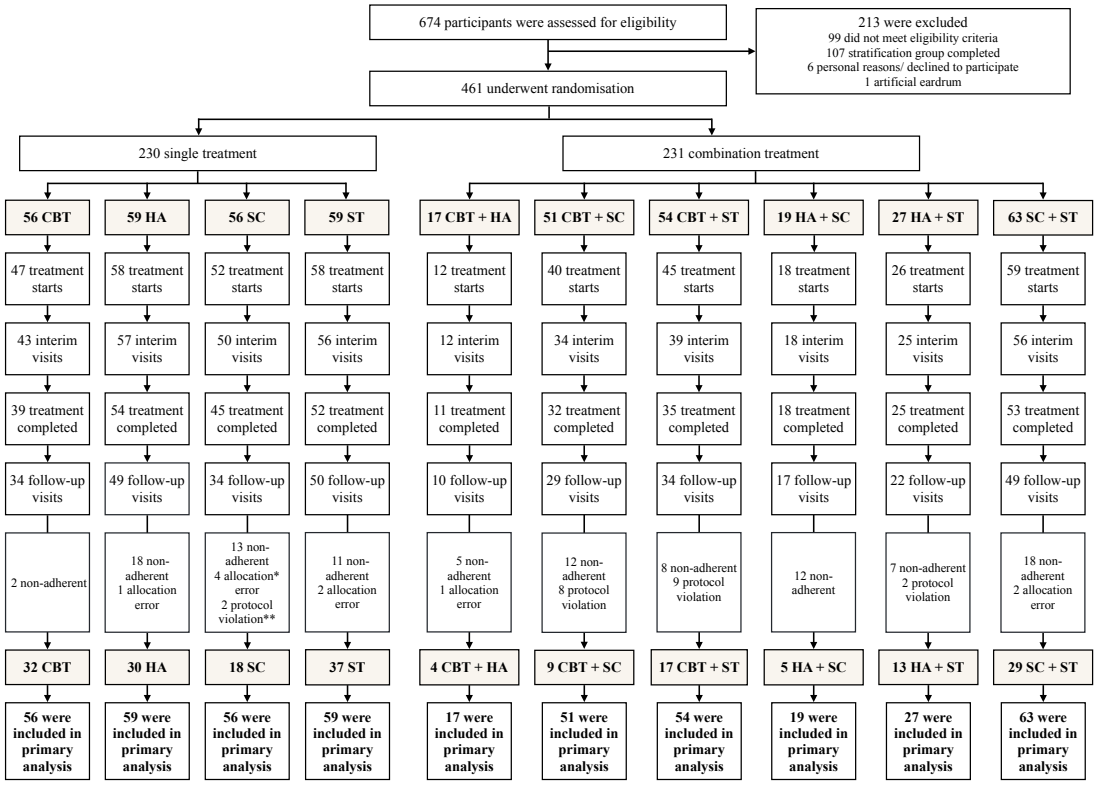
Structured Counselling + Sound Therapy



Single versus Combination Treatment in Tinnitus: An International, Multicentre, Parallel-arm, Superiority, Randomised Controlled Trial

Table Of Contents for Supplementary Appendix

1. *Figure S1: Extended Patients Flowchart (Intention-to-treat and Per-protocol Sample)*



Note. A total of 674 patient were screened of whom 461 (ITT sample) met the trial inclusion criteria and were randomly assigned to one of ten treatment arms comprised of a single treatment or a combination of two treatments using a set of four different therapy approaches - cognitive-behavioural therapy (CBT), hearing aids (HA), structured counselling (SC), and sound therapy (ST). 230 were assigned to single treatments and 231 were assigned to combination treatments. 213 subjects were excluded during the screening process. Available data for the primary outcome (incl. missing data) per study visit and treatment arm can be seen. The number of treatment non-adherence, protocol violations and allocation errors are equally shown per treatment arm. From the sample of 194 patients for the per-protocol analysis, nine had missings in covariates relevant for the analysis, resulting in a sample of 185 patients used for the per-protocol analysis. *Two allocation errors **one protocol violation were already lost to follow-up – those wore not subtracted at this stage.

2. *Table S1: Excluded Patients from Study Participation*

	N
Not meeting inclusion criteria	
Primary complaint tinnitus	2
Chronic tinnitus (≥ six months)	1
Age between 18 and 80 years	2
A score of ≥ 18 in the Tinnitus Handicap Inventory (THI; Newman et al., 1996) – at least mild tinnitus distress	32
A score of > 22 in the Montreal Cognitive Assessment (MoCa; Nasreddine et al., 2005) – absence of mild cognitive impairment	14
Ability and willingness to use the UNITI mobile applications on smartphones	4
Openness to use a HA (if indication and allocation to HA group)	..
Ability to understand and consent to the research (hearing ability, intellectual capacity)	..
Ability to participate in all relevant visits (no plans for e.g., long-term holidays or pregnancy)	..
Existing drug therapies with psychoactive substances (e.g., antidepressants or anticonvulsants) must be stable for at least 30 days at the beginning of the therapeutic intervention. The drug therapy should remain constant during the course of the study. Necessary changes do not constitute an exclusion criterion per se, but need to be recorded.	..
Meeting exclusion criteria	
Objective tinnitus or heartbeat-synchronous tinnitus as primary complaint	7
Otosclerosis / acoustic neuroma or other relevant ear disorders with fluctuation hearing	10
Present acute infections (acute otitis media, otitis externa, acute sinusitis)	1
Meniere's disease or similar syndromes (but not vestibular migraine)	2
Serious internal, neurological or psychiatric conditions	4
Epilepsy or other disorders of the central nervous system (e.g., brain tumor or encephalitis)	1
Clinically relevant drug, medication or alcohol abuse up to 12 weeks before study start	..
Severe hearing loss – inability to communicate properly in the course of the study	11
One deaf ear	4
Missing written informed consent	1
Start of any other tinnitus related treatments, especially hearing aids, structured counselling, sound therapy (with special devices; expecting long term effects) or cognitive behavioural therapy in the last 3 months before the start of the study	3
Other reasons	
Stratification group completed	107
Personal reasons/ declined to participate	6
Artificial eardrum	1
Total number of excluded patients	213

Note. We aimed for four equally sized stratification groups of 25 patients per clinical site. 107 patients could not be included in the trial since the respective stratification group (e.g., high tinnitus-related handicap and no hearing aid indication) was already full.

3. Table S2: Quantity and Reasons of Dropouts before Treatment Start per Treatment Arm

Treatment arm	N	Reasons (N)
CBT	9	No time (2); unable to travel to clinic (2); rejected CBT (2); no internet connection (1); started another treatment (1); interested in HA (1)
HA	1	Declined to participate (1)
SC	4	Rejected SC (1); interested in HA (1); declined to participate (1); app treatment not started (1)
ST	1	No capacity for daily app usage (1)
CBT + HA	5	Unable to travel to clinic (1); rejected HA and CBT (1); No capacity for CBT (1); suspected Morbus Meniere (1); lost (1)
CBT + SC	11	No time (4); lost (2); financial reasons (1); job reasons (1); chronic fatigue syndrome (1); rejected CBT (1); rejected CBT & app treatment not started (1)
CBT + ST	9	Rejected CBT + ST (3); no time (3); lost (1); personal reasons (1); job reasons (1)
HA + SC	1	Unexpected personal problems (1)
HA + ST	1	Rejected HA (1)
SC + ST	4	Interested in HA (1); no time (1); suspected acoustic neuroma (1); app treatment not started (1)
Total number of dropouts before treatment start	46	

Note. CBT = Cognitive-Behavioural Therapy; HA = Hearing Aids; SC = Structured Counselling; ST = Sound Therapy.

4. *Table S3: Quantity and Reasons of Dropouts during Treatment per Treatment Arm – before Interim Visit*

Treatment arm	N	Reasons (N)
CBT	4	Issues with daily app measures (1); no time (1); health worsening (1); personal reasons (1)
HA	1	Rejected HA (1)
SC	2	Not satisfied with treatment (1); lack of benefit & issues with daily app measures (1)
ST	3	Tinnitus worsening (1); tinnitus worsening & not satisfied with app treatment; no time due to illness (1)
CBT + HA	..	..
CBT + SC	6	Unsatisfied with CBT (1); health reasons (1); lost (1); no benefit of CBT (1); job reasons (1); rejected CBT (1)
CBT + ST	6	Tinnitus worsening (1); lost (1); no time (1); unable to travel to clinic (1); rejected CBT (1); treatment termination after first CBT session (1)
HA + SC	..	..
HA + ST	..	..
SC + ST	3	Tinnitus worsening (1); no reasons (1); lost (1)
Total number of dropouts during treatment – before interim visit	25	

Note. CBT = Cognitive-Behavioural Therapy; HA = Hearing Aids; SC = Structured Counselling; ST = Sound Therapy.

5. *Table S4: Quantity and Reasons of Dropouts during Treatment per Treatment Arm – after Interim Visit*

Treatment arm	N	Reasons (N)
CBT	4	No time (2); unable to travel to clinic (1); job reasons (1)
HA	3	Lost (2); started another HA treatment (1)
SC	5	Tinnitus worsening (1); lost (1); lack of benefit (1); health worsening/ reasons (1); did not want to continue (1)
ST	3	Not satisfied with treatment (2); lost (1)
CBT + HA	1	No time (1)
CBT + SC	2	No time (1); no longer attends CBT sessions (1)
CBT + ST	4	No benefit of CBT (2); tinnitus worsening (1); lost (1)
HA + SC	..	..
HA + ST	1	App treatment was never started (1)
SC + ST	3	App treatment was never started (1); lost (1); did not want to come to clinic due to COVID-19 pandemic (1)
Total number of dropouts during treatment – after interim visit	26	

Note. CBT = Cognitive-Behavioural Therapy; HA = Hearing Aids; SC = Structured Counselling; ST = Sound Therapy.

6. *Table S5: Quantity and Reasons of Patients lost to Follow-up*

Treatment arm	N	Reasons (N)
CBT	5	No response (3); health reasons (1); no reasons (1)
HA	5	Job reasons (2); no response (2); no reasons (1)
SC	11	No response (6); not interested in follow-up (3); no reasons (1); health reasons (1)
ST	2	No response (1); not available for follow-up (1)
CBT + HA	1	No response (1)
CBT + SC	3	No response (1); not interested in follow-up (1); terminated follow-up too late (1)
CBT + ST	1	Deceased (1)
HA + SC	1	No response (1)
HA + ST	3	No response (3)
SC + ST	4	No response (2); wanted to discontinue (1); not available for follow-up (1)
Total number of patients lost to follow-up	36	

Note. CBT = Cognitive-Behavioural Therapy; HA = Hearing Aids; SC = Structured Counselling; ST = Sound Therapy.

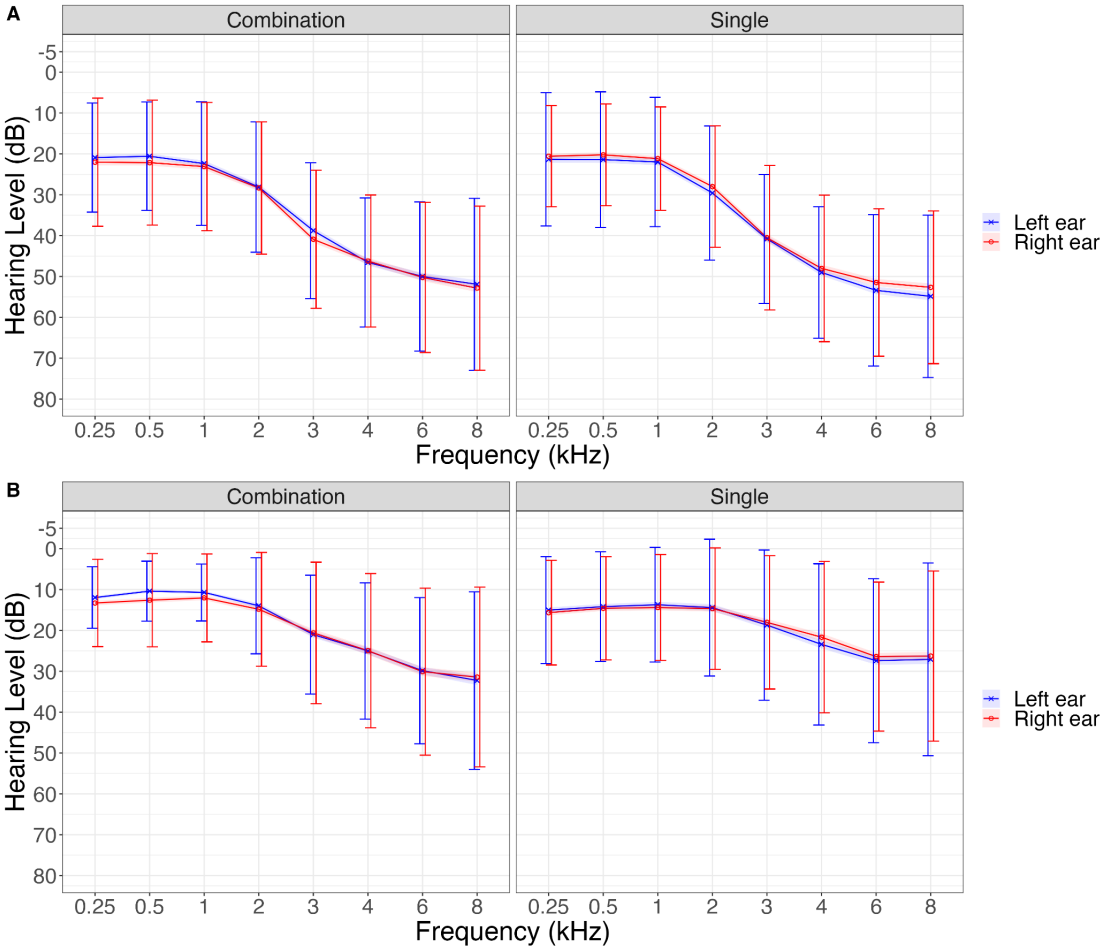
7. *Table S6: Demographic and Clinical Characteristics of the Participants at Baseline (stratified by Treatment Arm).*

	CBT (n=56)	HA (n=59)	SC (n=56)	ST (n=59)	CBT + HA (n=17)	CBT + SC (n=51)	CBT + ST (n=54)	HA + SC (N=19)	HA + ST (n=27)	SC + ST (n=63)	Total (N=461)
Education — no. (%)											
Elementary or middle school	11 (21.2%)	18 (30.5%)	12 (21.8%)	12 (21.4%)	7 (43.8%)	20 (41.7%)	10 (20.0%)	4 (21.1%)	6 (22.2%)	17 (27.0%)	117 (26.3%)
High school	10 (19.2%)	10 (16.9%)	12 (21.8%)	16 (28.6%)	2 (12.5%)	7 (14.6%)	11 (22.0%)	6 (31.6%)	6 (22.2%)	13 (20.6%)	93 (20.9%)
University	31 (59.6%)	31 (52.5%)	31 (56.4%)	28 (50.0%)	7 (43.8%)	21 (43.8%)	29 (58.0%)	9 (47.4%)	15 (55.6%)	33 (52.4%)	235 (52.8%)
Tinnitus Presentation (ESIT-SQ B2) — no. (%)											
constant	48 (94.1%)	57 (96.6%)	49 (92.5%)	51 (94.4%)	13 (86.7%)	44 (93.6%)	45 (93.8%)	18 (100%)	26 (100%)	57 (90.5%)	408 (94.0%)
intermittent	3 (5.88%)	2 (3.39%)	4 (7.55%)	3 (5.56%)	2 (13.3%)	3 (6.38%)	3 (6.25%)	0 (0%)	0 (0%)	6 (9.52%)	26 (5.99%)
Tinnitus Loudness [dB] (Tinnitus Matching)											
Mean (SD)	35.3 (21.6)	42.0 (21.1)	32.8 (23.0)	37.4 (23.1)	48.7 (18.6)	37.9 (19.1)	37.4 (18.6)	44.9 (27.6)	51.4 (19.9)	38.0 (21.8)	38.8 (21.7)
Median [Min, Max]	37.3 [1, 83]	46.0 [0, 82.5]	30.0 [2.5, 88]	35.0 [5, 90]	48.0 [20, 78]	40.5 [0, 75]	35.0 [5, 85]	41.3 [0, 100]	53.8 [10, 95]	35.0 [2.50, 92]	40.0 [0, 100]
Residual inhibition: Both ears — no. (%)											
none	17 (70.8%)	10 (41.7%)	11 (45.8%)	16 (50.0%)	3 (42.9%)	14 (56.0%)	17 (53.1%)	5 (50.0%)	8 (57.1%)	17 (48.6%)	118 (52.0%)
partially	5 (20.8%)	10 (41.7%)	8 (33.3%)	8 (25.0%)	2 (28.6%)	5 (20.0%)	7 (21.9%)	4 (40.0%)	5 (35.7%)	7 (20.0%)	61 (26.9%)
complete	2 (8.33%)	4 (16.7%)	5 (20.8%)	8 (25.0%)	2 (28.6%)	6 (24.0%)	8 (25.0%)	1 (10.0%)	1 (7.14%)	11 (31.4%)	48 (21.1%)
Residual inhibition: Left ear — no. (%)											
none	9 (50.0%)	10 (62.5%)	9 (56.3%)	10 (71.4%)	2 (66.7%)	7 (63.6%)	7 (70.0%)	3 (75.0%)	1 (16.7%)	4 (33.3%)	62 (56.4%)
partially	5 (27.8%)	2 (12.5%)	1 (6.25%)	2 (14.3%)	0 (0%)	2 (18.2%)	1 (10.0%)	1 (25.0%)	3 (50.0%)	6 (50.0%)	23 (20.9%)

	CBT (n=56)	HA (n=59)	SC (n=56)	ST (n=59)	CBT + HA (n=17)	CBT + SC (n=51)	CBT + ST (n=54)	HA + SC (N=19)	HA + ST (n=27)	SC + ST (n=63)	Total (N=461)
complete	4 (22.2%)	4 (25.0%)	6 (37.5%)	2 (14.3%)	1 (33.3%)	2 (18.2%)	2 (20.0%)	0 (0%)	2 (33.3%)	2 (16.7%)	25 (22.7%)
Residual inhibition: Right ear — no. (%)											
none	9 (60.0%)	12 (63.2%)	11 (78.6%)	10 (90.9%)	5 (83.3%)	10 (66.7%)	6 (75.0%)	3 (60.0%)	3 (60.0%)	6 (54.5%)	75 (68.8%)
partially	2 (13.3%)	4 (21.1%)	1 (7.14%)	0 (0%)	0 (0%)	1 (6.67%)	1 (12.5%)	2 (40.0%)	0 (0%)	3 (27.3%)	14 (12.8%)
complete	4 (26.7%)	3 (15.8%)	2 (14.3%)	1 (9.09%)	1 (16.7%)	4 (26.7%)	1 (12.5%)	0 (0%)	2 (40.0%)	2 (18.2%)	20 (18.3%)
WHO-QoL 1 score: Physical health											
Mean (SD)	12.4 (1.73)	12.5 (1.78)	12.4 (1.84)	11.8 (2.10)	13.0 (1.62)	12.9 (2.04)	12.6 (1.57)	13.1 (1.26)	12.7 (2.11)	12.7 (1.96)	12.5 (1.87)
Median [Min, Max]	13.0 [7, 15]	13.0 [7, 15]	13.0 [7, 17]	11.5 [7, 16]	13.0 [10, 16]	13.0 [9, 17]	13.0 [10, 15]	13.0 [11, 15]	13.0 [10, 17]	13.0 [8, 17]	13.0 [7, 17]
WHO-QoL 2 score: Psychological health											
Mean (SD)	13.3 (1.92)	13.6 (1.61)	13.5 (1.99)	13.2 (2.02)	13.9 (1.03)	14.1 (1.84)	13.7 (1.72)	14.2 (1.48)	13.3 (2.09)	13.5 (1.95)	13.6 (1.85)
Median [Min, Max]	13.0 [8, 17]	14.0 [9, 16]	14.0 [9, 18]	13.0 [6, 17]	14.0 [12, 16]	14.0 [10, 17]	14.0 [11, 17]	14.0 [11, 17]	13.0 [8, 17]	14.0 [9, 17]	14.0 [6, 18]
WHO-QoL 3 score: Social factors											
Mean (SD)	14.5 (3.27)	14.3 (3.15)	14.5 (3.03)	14.0 (3.11)	14.6 (2.83)	14.8 (3.01)	14.6 (3.15)	15.1 (2.78)	14.6 (3.14)	14.9 (2.96)	14.5 (3.06)
Median [Min, Max]	15.0 [8, 20]	15.0 [5, 20]	15.0 [8, 20]	15.0 [4, 20]	15.0 [9, 20]	15.0 [8, 20]	15.0 [9, 20]	15.5 [9, 20]	15.0 [8, 20]	16.0 [7, 20]	15.0 [4, 20]
WHO-QoL 4 score: Environment											
Mean (SD)	15.8 (2.09)	15.9 (2.15)	15.7 (2.59)	15.5 (2.35)	16.1 (1.82)	16.4 (1.93)	15.6 (1.92)	15.8 (1.77)	15.7 (2.38)	16.0 (2.30)	15.8 (2.18)
Median [Min, Max]	16.0 [11, 20]	16.0 [8, 20]	16.0 [9, 20]	15.5 [9, 20]	16.0 [13, 19]	16.0 [13, 20]	16.0 [12, 20]	15.5 [13, 19]	16.0 [11, 20]	16.0 [12, 20]	16.0 [8, 20]

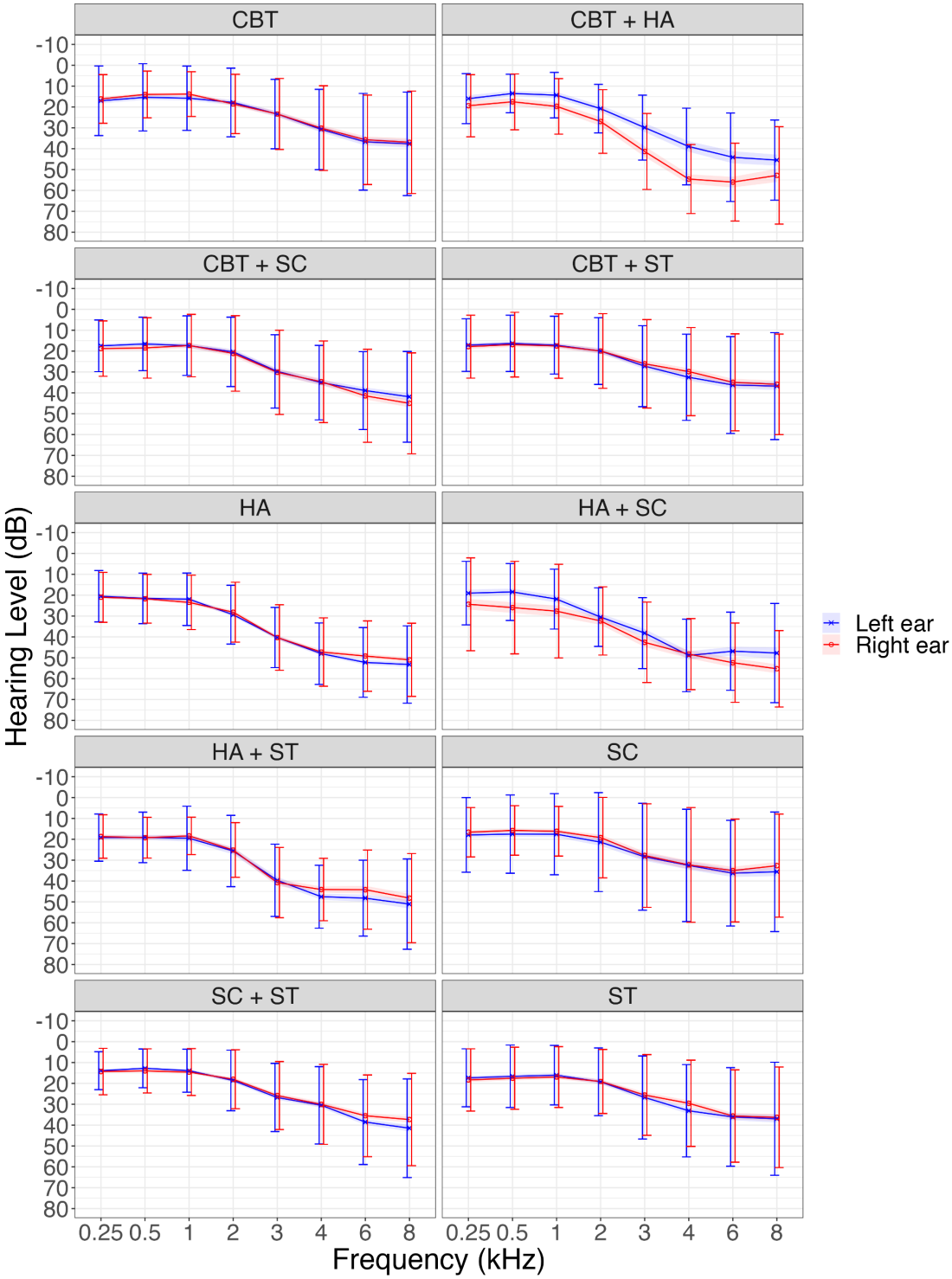
Note. Data are n (%), mean (SD), or median [Min, Max]. Tinnitus loudness level in dB was obtained by tinnitus matching, with higher values indicating greater perceived tinnitus loudness. Residual inhibition is the brief tinnitus suppression following acoustic stimulation. WHO-QoL scores range from 4 to 20, with higher scores indicating higher quality of life in the respective domain. CBT = Cognitive-Behavioural Therapy; HA = Hearing Aids; SC = Structured Counselling; ST = Sound Therapy.

8. *Figure S2: Audiogram in Patients with and Without Hearing Aid Indication for Single and Combined Treatment Groups*



Note. Pooled audiogram for patients (A) with hearing aid indication and (B) without hearing aid indication separated for single and combined treatment groups measured by pure tone audiometry at baseline visit according to the guidelines of the British Society of Audiology. Error bars represent standard deviation.

9. *Figure S3: Audiogram for Patients in all Treatment Groups*



Note. Pooled audiograms of patients in all treatment groups measured by pure tone audiometry at baseline visit according to the guidelines of the British Society of Audiology. Error bars represent standard deviation. CBT = Cognitive-Behavioural Therapy; HA = Hearing Aids; SC = Structured Counselling; ST = Sound Therapy.

10. Table S7: Representativeness of Study Participants

Category	**Example**
Condition under investigation	Chronic tinnitus. The Tinnitus persisted for a minimum of 6 months.
Sex	No sex effect was found for the primary outcome (THI) when comparing single versus combination treatments for chronic tinnitus. 41.2 % of the participants were female, 58.8% were male.
Age	No age effect was found for the primary outcome (THI) when comparing single versus combination treatments for chronic tinnitus. The average age was 51.1 years. In a study by Probst et al. 2017, it was reported that the majority of patients visiting the specialised tinnitus clinic in Regensburg are in the age range of 45 - 55 years.
Race or ethnic group	Race or ethnicity was not assessed. No conclusions can be drawn about the influence of race or ethnicity.
Geography	The 5 centres were located in four European countries: Germany (2), Greece, Netherlands, Spain. Conclusions about countries with dissimilar health care systems are limited.
Severity	The average THI score at baseline was 48.0, which is considered moderate tinnitus distress. Participants with slight or no distress at screening (THI < 18), were excluded from the study.
Other considerations	In this trial, we compared single versus combination treatment of four clinical intervention types typically used for tinnitus treatment: cognitive behavioural therapy, hearing aids, sound therapy, and structured counselling for a duration of 12 weeks. The treatments were implemented in a typical way. Conclusions about treatments with different implementations are limited.
Overall representativeness of this trial	This trial showed that combining a treatment of weak clinical efficacy with a treatment of stronger clinical efficacy leads to an improvement of the overall clinical outcome. We recognise that the trial was limited to only four different clinical intervention types and their combinations. We do not know whether other treatment combinations, which are not part of the trial, would be superior to their respective singe treatments. We cannot conclude about combination treatments with three or more clinical interventions. All treatments were implemented in a typical way; however, it would be possible to implement them differently or apply the treatment for a shorter or longer time. We do not know whether other implementation would have the same results.

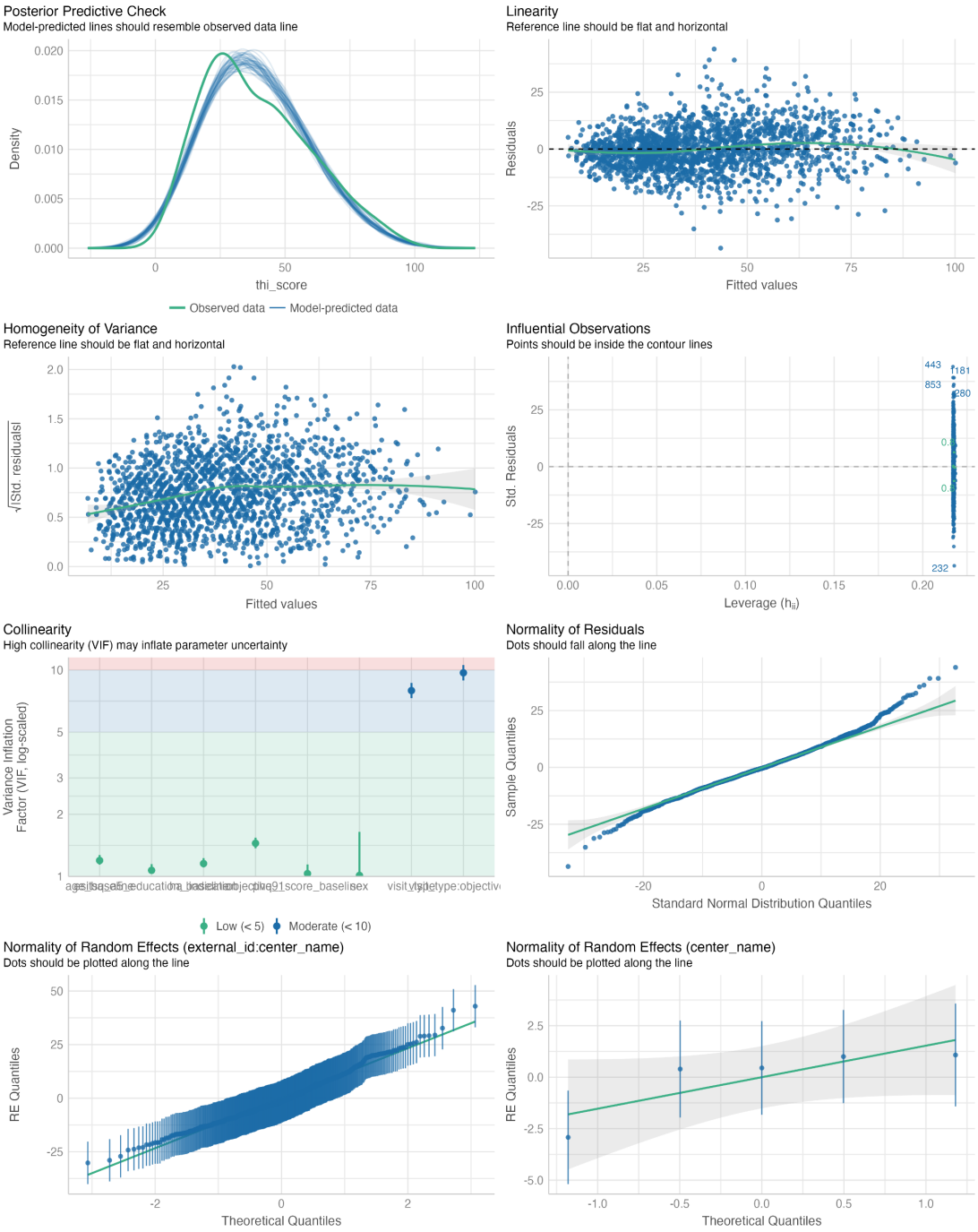
11. *Table S8: Primary Outcome (THI) Objective 1: Model parameters*

Characteristic	Beta	95% CI[1]	p-value
visit_type			
baseline	—	—	
interim_visit	-10.497	-12.622, -8.373	**<0.001**
final_visit	-14.864	-16.998, -12.730	**<0.001**
followup_1	-13.306	-15.522, -11.090	**<0.001**
objective_1			
Combination	—	—	
Single	-0.178	-3.293, 2.938	0.911
sex			
female	—	—	
male	-0.891	-3.690, 1.908	0.532
age_baseline	-0.034	-0.154, 0.086	0.575
ha_indication			
ha	—	—	
no_ha	-3.509	-6.367, -0.650	**0.016**
phq9_score_baseline	2.132	1.852, 2.411	**<0.001**
esitsq_a5_education_baseline			
elementary_middle	—	—	
high_school	1.949	-2.182, 6.079	0.355
university	-3.428	-6.921, 0.065	0.054
visit_type * objective_1			
interim_visit * Single	2.647	-0.376, 5.669	0.086
final_visit * Single	3.159	0.235, 6.083	**0.034**
followup_1 * Single	1.382	-1.632, 4.396	0.368

[1] CI = Confidence Interval

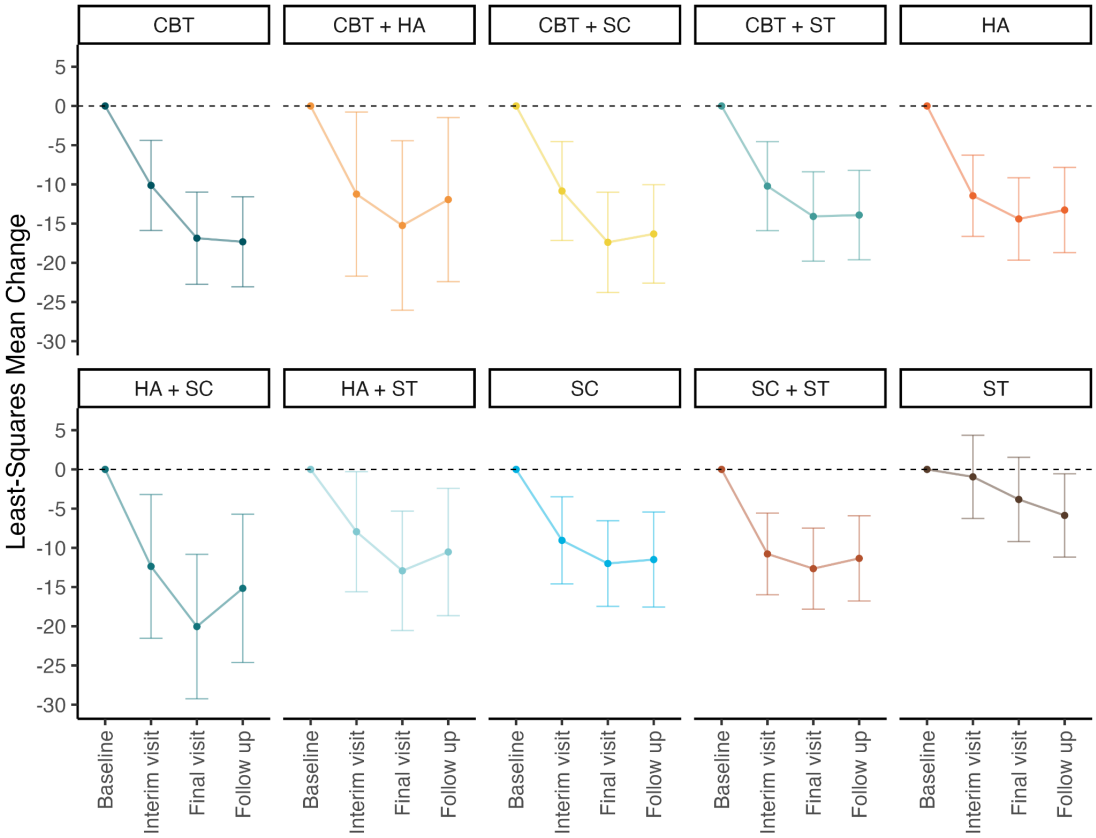
Note. The table depicts the parameters of the linear mixed effects model (using REML in the lme4 R package) predicting the primary outcome by objective, time point (baseline, interim visit, final visit, and follow-up), and objective-by-time interaction as fixed effects, including centre and subject ID as random intercepts. The model was adjusted for the following covariates: age, sex, educational attainment, hearing aid indication, and PHQ-9 baseline scores. All comparisons are two-sided and p values reported here were not adjusted for multiple comparisons.

12. *Figure S4: Primary Outcome (THI) Objective 1: Model Assumptions*



Note. Model assumptions are plotted for the first of the 50 imputed datasets.

13. *Figure S5: Primary Outcome (THI) Objective 2*



Note. Total THI scores range from 0 to 100, with higher scores indicating greater severity of tinnitus. Error bars represent 95% confidence intervals. Sample sizes: CBT: N = 56, HA: N = 59, SC: N = 56, ST: N = 59, CBT + HA: N = 17, CBT + SC: N = 51, CBT + ST: N = 54, HA + SC: N = 19, HA + ST: N = 27, SC + ST: N = 63. CBT = Cognitive-Behavioural Therapy; HA = Hearing Aids; SC = Structured Counselling; ST = Sound Therapy.

14. Table S9: THI Change from Baseline to Final Visit for Hearing Aid Indication (yes/no)

Contrast	Change from baseline (Hearing aid indication: yes)	Change from baseline (Hearing aid indication: no)
CBT	-10.4 [-20.9, 0]	-20.2 [-27.1, -13.2]
CBT + HA	-15.2 [-26, -4.5]	NA
CBT + SC	-18.6 [-28.3, -8.9]	-16.7 [-25.1, -8.4]
CBT + ST	-11.4 [-21.3, -1.6]	-15.3 [-22.4, -8.2]
HA	-14.4 [-19.6, -9.2]	NA
HA + SC	-20 [-29.2, -10.9]	NA
HA + ST	-12.9 [-20.5, -5.4]	NA
SC	-12.8 [-22.5, -3.1]	-11.6 [-18.3, -4.8]
SC + ST	-13.1 [-22.4, -3.9]	-12.5 [-18.7, -6.3]
ST	-3 [-12, 6.1]	-4.3 [-10.9, 2.4]

Note. Values depict least-squares mean changes with 95% CI in square brackets. CBT = Cognitive-Behavioural Therapy; HA = Hearing Aids; SC = Structured Counselling; ST = Sound Therapy.

15. Table S10: THI Change from Baseline to Final Visit for High and Low Tinnitus Distress Severity

Contrast	Change from baseline (High tinnitus distress severity)	Change from baseline (Low tinnitus distress severity)
CBT	-25 [-34.2, -15.8]	-9.3 [-16, -2.5]
CBT + HA	-18.7 [-36.6, -0.8]	-12.2 [-24, -0.3]
CBT + SC	-24.4 [-33.7, -15.1]	-10.6 [-18.6, -2.6]
CBT + ST	-23.2 [-32.2, -14.3]	-6.2 [-13.1, 0.7]
HA	-18.1 [-26.1, -10.1]	-10.6 [-17.2, -4.1]
HA + SC	-26.9 [-41.6, -12.2]	-13.8 [-24.5, -3.2]
HA + ST	-12.8 [-24.4, -1.2]	-13.1 [-22.4, -3.8]
SC	-15.6 [-24.6, -6.7]	-8.8 [-15.2, -2.5]
SC + ST	-19.1 [-27.8, -10.5]	-7.8 [-13.5, -2.1]
ST	-6.3 [-14.6, 2.1]	-1.5 [-7.8, 4.8]

Note. Values depict least-squares mean changes with 95% CI in square brackets. High tinnitus distress severity: THI ≥ 48 at Screening. Low tinnitus distress severity: THI < 48 at Screening. CBT = Cognitive-Behavioural Therapy; HA = Hearing Aids; SC = Structured Counselling; ST = Sound Therapy.

16. Table S11: Primary Outcome (THI) Objective 4 & 5 at Final Visit

Objective	Contrast	Change from baseline	95% CI
4_A	Doesnt_have_CBT	-11.57	[-14.01, -9.14]
4_A	Has_CBT	-16.02	[-19.33, -12.70]
4_B	Doesnt_have_HA	-11.42	[-15.47, -7.38]
4_B	Has_HA	-15.07	[-18.75, -11.39]
4_C	Doesnt_have_SC	-12.46	[-15.01, -9.91]
4_C	Has_SC	-14.48	[-17.62, -11.34]
4_D	Doesnt_have_ST	-15.48	[-18.23, -12.72]
4_D	Has_ST	-10.51	[-13.43, -7.58]
5	Brain	-15.36	[-18.82, -11.89]
5	Brain_and_Ear	-14.36	[-17.69, -11.04]
5	Ear	-9.83	[-13.20, -6.45]

Note. Values depict least-squares mean changes with 95% CI in square brackets. Objective 4: Treatments with vs. treatments without; Objective 5: Ear mediated vs. brain mediated vs. ear and brain mediated treatments. CBT = Cognitive-Behavioural Therapy; HA = Hearing Aids; SC = Structured Counselling; ST = Sound Therapy.

17. Table S12: Primary Outcome (THI) at Interim Visit

Objective	Contrast	Change from baseline	95% CI
1	Combination	-10.50	[-13.28, -7.71]
1	Single	-7.85	[-10.66, -5.04]
2	CBT	-10.13	[-15.87, -4.38]
2	CBT + HA	-11.24	[-21.70, -0.78]
2	CBT + SC	-10.84	[-17.15, -4.54]
2	CBT + ST	-10.22	[-15.90, -4.55]
2	HA	-11.45	[-16.63, -6.27]
2	HA + SC	-12.37	[-21.53, -3.21]
2	HA + ST	-7.95	[-15.61, -0.29]
2	SC	-9.05	[-14.60, -3.50]
2	SC + ST	-10.78	[-15.99, -5.57]
2	ST	-0.95	[-6.25, 4.35]
3_A	Combi_CBT	-10.62	[-14.57, -6.68]
3_A	Single_CBT	-10.13	[-15.92, -4.33]
3_B	Combi_HA	-10.17	[-15.05, -5.28]
3_B	Single_HA	-11.45	[-16.42, -6.48]
3_C	Combi_SC	-11.03	[-14.72, -7.34]
3_C	Single_SC	-9.05	[-14.60, -3.50]
3_D	Combi_ST	-10.04	[-13.57, -6.51]
3_D	Single_ST	-0.95	[-6.35, 4.46]
4_A	Doesnt_have_CBT	-8.36	[-10.83, -5.90]
4_A	Has_CBT	-10.47	[-13.70, -7.23]
4_B	Doesnt_have_HA	-7.77	[-11.79, -3.76]
4_B	Has_HA	-10.79	[-14.39, -7.19]
4_C	Doesnt_have_SC	-8.30	[-10.87, -5.72]
4_C	Has_SC	-10.44	[-13.54, -7.35]
4_D	Doesnt_have_ST	-10.58	[-13.23, -7.92]
4_D	Has_ST	-7.40	[-10.34, -4.45]
5	Brain	-9.98	[-13.33, -6.63]
5	Brain_and_Ear	-10.83	[-14.19, -7.47]
5	Ear	-6.53	[-9.91, -3.14]

Note. Values depict least-squares mean changes with 95% CI in square brackets. Objective 1: Single vs. Combination (all treatments); Objective 2: All treatments against each other; Objective 3: Single vs. Combination (separately); Objective 4: Treatments with vs. treatments without; Objective 5: Ear-mediated vs. brain-mediated vs. ear- and brain-mediated treatments. CBT = Cognitive-Behavioural Therapy; HA = Hearing Aids; SC = Structured Counselling; ST = Sound Therapy.

18. Table S13: Primary Outcome (THI) at Follow-up

Objective	Contrast	Change from baseline	95% CI
1	Combination	-13.31	[-16.21, -10.40]
1	Single	-11.92	[-14.75, -9.09]
2	CBT	-17.32	[-23.06, -11.58]
2	CBT + HA	-11.94	[-22.40, -1.48]
2	CBT + SC	-16.32	[-22.60, -10.04]
2	CBT + ST	-13.91	[-19.62, -8.20]
2	HA	-13.27	[-18.70, -7.83]
2	HA + SC	-15.17	[-24.62, -5.71]
2	HA + ST	-10.53	[-18.65, -2.41]
2	SC	-11.50	[-17.55, -5.44]
2	SC + ST	-11.35	[-16.77, -5.92]
2	ST	-5.87	[-11.18, -0.55]
3_A	Combi_CBT	-14.64	[-18.56, -10.72]
3_A	Single_CBT	-17.32	[-23.11, -11.53]
3_B	Combi_HA	-12.31	[-17.40, -7.21]
3_B	Single_HA	-13.27	[-18.51, -8.03]
3_C	Combi_SC	-13.80	[-17.67, -9.93]
3_C	Single_SC	-11.50	[-17.55, -5.44]
3_D	Combi_ST	-12.15	[-15.79, -8.52]
3_D	Single_ST	-5.87	[-11.28, -0.45]
4_A	Doesnt_have_CBT	-10.81	[-13.39, -8.23]
4_A	Has_CBT	-15.49	[-18.75, -12.22]
4_B	Doesnt_have_HA	-11.46	[-15.62, -7.29]
4_B	Has_HA	-12.77	[-16.59, -8.95]
4_C	Doesnt_have_SC	-12.27	[-14.90, -9.64]
4_C	Has_SC	-13.12	[-16.48, -9.75]
4_D	Doesnt_have_ST	-14.42	[-17.15, -11.69]
4_D	Has_ST	-10.33	[-13.30, -7.36]
5	Brain	-15.01	[-18.56, -11.45]
5	Brain_and_Ear	-12.79	[-16.23, -9.35]
5	Ear	-9.75	[-13.22, -6.28]

Note. Values depict least-squares mean changes with 95% CI in square brackets. Objective 1: Single vs. Combination (all treatments); Objective 2: All treatments against each other; Objective 3: Single vs. Combination (separately); Objective 4: Treatments with vs. treatments without; Objective 5: Ear-mediated vs. brain-mediated vs. ear- and brain-mediated treatments. CBT = Cognitive-Behavioural Therapy; HA = Hearing Aids; SC = Structured Counselling; ST = Sound Therapy.

19. Table S14: THI Change from Baseline to Final Visit for each Country

Contrast	Belgium	Germany	Greece	Spain
Single	-9.4 [-3.2; -15.5]	-12.0 [-8.0; -16.0]	-16.0 [-9.2; -22.8]	-8.8 [-2.4; -15.2]
Combination	-13.1 [-4.9; -21.2]	-16.5 [-12.6; -20.4]	-15.8 [-9.3; -22.3]	-11.3 [-5.1; -17.5]
CBT	-19.1 [-5.7; -32.4]	-16.4 [-8.0; -24.8]	-20.4 [-6.8; -34.0]	-11.4 [2.6; -25.5]
CBT + HA	-38.0 [0.7; -76.7]	-14.1 [0.8; -29.1]	-11.1 [14.8; -37.0]	-16.0 [5.7; -37.6]
CBT + SC	-13.7 [6.5; -33.9]	-21.1 [-12.8; -29.4]	-15.7 [-2.0; -29.5]	-12.2 [2.8; -27.3]
CBT + ST	-12.9 [5.8; -31.6]	-17.5 [-10.0; -25.0]	-11.8 [2.2; -25.7]	-10.1 [2.3; -22.6]
HA	-12.6 [-1.1; -24.2]	-15.5 [-8.2; -22.8]	-21.2 [-7.5; -34.8]	-7.8 [5.0; -20.6]
HA + SC	-26.7 [-2.0; -51.5]	-19.5 [-6.8; -32.2]	-21.1 [2.3; -44.6]	-15.0 [4.6; -34.6]
HA + ST	4.7 [27.0; -17.7]	-9.9 [1.0; -20.9]	-30.3 [-12.6; -48.1]	-10.3 [5.6; -26.3]
SC	-7.1 [5.3; -19.5]	-12.7 [-4.8; -20.6]	-13.5 [0.3; -27.3]	-14.9 [-1.2; -28.5]
SC + ST	-11.5 [1.1; -24.1]	-14.2 [-6.9; -21.5]	-13.0 [-0.6; -25.5]	-9.3 [3.5; -22.0]
ST	-0.3 [11.5; -12.1]	-3.4 [4.0; -10.9]	-9.3 [4.1; -22.6]	-2.6 [10.4; -15.6]

Note. Values depict least-squares mean changes with 95% CI in square brackets. Comparison of single and combination treatments as well as all treatments regarding the THI difference from baseline to final visit for each country. Note that there were two centers in Germany (Berlin, Regensburg).

20. Table S15: Secondary Outcome (TFI) Objective 4 & 5 at Final Visit

Objective	Contrast	Change from baseline	95% CI
4_A	Doesnt_have_CBT	-10.01	[-12.66, -7.36]
4_A	Has_CBT	-13.33	[-16.89, -9.78]
4_B	Doesnt_have_HA	-9.25	[-13.64, -4.86]
4_B	Has_HA	-14.19	[-18.09, -10.29]
4_C	Doesnt_have_SC	-12.21	[-14.96, -9.46]
4_C	Has_SC	-9.97	[-13.33, -6.61]
4_D	Doesnt_have_ST	-12.80	[-15.62, -9.99]
4_D	Has_ST	-9.37	[-12.56, -6.18]
5	Brain	-12.26	[-15.89, -8.64]
5	Brain_and_Ear	-11.13	[-14.86, -7.40]
5	Ear	-10.37	[-14.00, -6.73]

Note. Values depict least-squares mean changes with 95% CI in square brackets. Objective 4: Treatments with vs. treatments without; Objective 5: Ear-mediated vs. brain-mediated vs. ear- and brain-mediated treatments. CBT = Cognitive-Behavioural Therapy; HA = Hearing Aids; SC = Structured Counselling; ST = Sound Therapy.

21. Table S16: Secondary Outcome (Mini-TQ) Objective 4 & 5 at Final Visit

Objective	Contrast	Change from baseline	95% CI
4_A	Doesnt_have_CBT	-2.63	[-3.25, -2.02]
4_A	Has_CBT	-3.91	[-4.71, -3.10]
4_B	Doesnt_have_HA	-2.51	[-3.49, -1.53]
4_B	Has_HA	-3.28	[-4.16, -2.41]
4_C	Doesnt_have_SC	-3.05	[-3.69, -2.41]
4_C	Has_SC	-3.23	[-3.99, -2.48]
4_D	Doesnt_have_ST	-3.61	[-4.27, -2.95]
4_D	Has_ST	-2.50	[-3.24, -1.77]
5	Brain	-3.65	[-4.50, -2.80]
5	Brain_and_Ear	-3.30	[-4.15, -2.44]
5	Ear	-2.35	[-3.21, -1.50]

Note. Values depict least-squares mean changes with 95% CI in square brackets. Objective 4: Treatments with vs. treatments without; Objective 5: Ear-mediated vs. brain-mediated vs. ear- and brain-mediated treatments. CBT = Cognitive-Behavioural Therapy; HA = Hearing Aids; SC = Structured Counselling; ST = Sound Therapy.

22. *Table S17: Secondary Outcome (NRS-2: "How strong or loud is your tinnitus at present?") Objective 4 & 5 at Final Visit*

Objective	Contrast	Change from baseline	95% CI
4_A	Doesnt_have_CBT	-0.80	[-1.15, -0.45]
4_A	Has_CBT	-0.73	[-1.21, -0.25]
4_B	Doesnt_have_HA	-0.44	[-1.03, 0.15]
4_B	Has_HA	-1.10	[-1.63, -0.57]
4_C	Doesnt_have_SC	-0.79	[-1.15, -0.42]
4_C	Has_SC	-0.76	[-1.20, -0.31]
4_D	Doesnt_have_ST	-0.87	[-1.27, -0.48]
4_D	Has_ST	-0.64	[-1.05, -0.24]
5	Brain	-0.75	[-1.26, -0.24]
5	Brain_and_Ear	-0.68	[-1.17, -0.19]
5	Ear	-0.90	[-1.38, -0.42]

Note. Values depict least-squares mean changes with 95% CI in square brackets. Objective 4: Treatments with vs. treatments without; Objective 5: Ear-mediated vs. brain-mediated vs. ear- and brain-mediated treatments. CBT = Cognitive-Behavioural Therapy; HA = Hearing Aids; SC = Structured Counselling; ST = Sound Therapy.

23. Table S18: Secondary Outcome (PHQ-9) Objective 4 & 5 at Final Visit

Objective	Contrast	Change from baseline	95% CI
4_A	Doesnt_have_CBT	-1.46	[-2.04, -0.88]
4_A	Has_CBT	-1.70	[-2.45, -0.95]
4_B	Doesnt_have_HA	-1.28	[-2.25, -0.32]
4_B	Has_HA	-1.90	[-2.76, -1.05]
4_C	Doesnt_have_SC	-1.62	[-2.22, -1.02]
4_C	Has_SC	-1.46	[-2.20, -0.73]
4_D	Doesnt_have_ST	-1.85	[-2.48, -1.23]
4_D	Has_ST	-1.17	[-1.87, -0.48]
5	Brain	-1.72	[-2.52, -0.93]
5	Brain_and_Ear	-1.36	[-2.17, -0.55]
5	Ear	-1.57	[-2.37, -0.77]

Note. Values depict least-squares mean changes with 95% CI in square brackets. Objective 4: Treatments with vs. treatments without; Objective 5: Ear-mediated vs. brain-mediated vs. ear- and brain-mediated treatments. CBT = Cognitive-Behavioural Therapy; HA = Hearing Aids; SC = Structured Counselling; ST = Sound Therapy.

24. Table S19: Secondary Outcome (WHO-QoL-Bref 1: Physical Health) at Final Visit

Objective	Contrast	Change from baseline	95% CI
1	Combination	0.29	[0.01, 0.58]
1	Single	0.42	[0.13, 0.71]
2	CBT	0.43	[-0.18, 1.04]
2	CBT + HA	0.49	[-0.64, 1.62]
2	CBT + SC	0.24	[-0.39, 0.88]
2	CBT + ST	0.36	[-0.23, 0.95]
2	HA	0.52	[-0.01, 1.06]
2	HA + SC	0.64	[-0.32, 1.60]
2	HA + ST	0.36	[-0.43, 1.15]
2	SC	0.20	[-0.39, 0.79]
2	SC + ST	0.10	[-0.44, 0.63]
2	ST	0.51	[-0.04, 1.07]
3_A	Combi_CBT	0.33	[-0.07, 0.73]
3_A	Single_CBT	0.43	[-0.17, 1.03]
3_B	Combi_HA	0.48	[-0.06, 1.01]
3_B	Single_HA	0.52	[-0.01, 1.06]
3_C	Combi_SC	0.23	[-0.15, 0.60]
3_C	Single_SC	0.20	[-0.38, 0.79]
3_D	Combi_ST	0.24	[-0.12, 0.61]
3_D	Single_ST	0.51	[-0.05, 1.07]
4_A	Doesnt_have_CBT	0.35	[0.10, 0.61]
4_A	Has_CBT	0.36	[0.02, 0.70]
4_B	Doesnt_have_HA	0.34	[-0.08, 0.75]
4_B	Has_HA	0.50	[0.13, 0.87]
4_C	Doesnt_have_SC	0.45	[0.18, 0.72]
4_C	Has_SC	0.22	[-0.10, 0.54]
4_D	Doesnt_have_ST	0.38	[0.11, 0.66]
4_D	Has_ST	0.32	[0.02, 0.62]
5	Brain	0.29	[-0.06, 0.64]
5	Brain_and_Ear	0.30	[-0.05, 0.65]
5	Ear	0.49	[0.14, 0.84]

Note. Values depict least-squares mean changes with 95% CI in square brackets. Objective 1: Single vs. Combination (all treatments); Objective 2: All treatments against each other; Objective 3: Single vs. Combination (separately); Objective 4: Treatments with vs. treatments without; Objective 5: Ear-mediated vs. brain-mediated vs. ear- and brain-mediated treatments. CBT = Cognitive-Behavioural Therapy; HA = Hearing Aids; SC = Structured Counselling; ST = Sound Therapy.

25. Table S20: Secondary Outcome (WHO-QoL-Bref 2: Psychological Health) at Final Visit

Objective	Contrast	Change from baseline	95% CI
1	Combination	0.36	[0.07, 0.65]
1	Single	0.36	[0.08, 0.65]
2	CBT	0.33	[-0.25, 0.92]
2	CBT + HA	0.75	[-0.35, 1.86]
2	CBT + SC	0.28	[-0.35, 0.91]
2	CBT + ST	0.35	[-0.27, 0.97]
2	HA	0.35	[-0.18, 0.89]
2	HA + SC	0.15	[-0.81, 1.10]
2	HA + ST	0.41	[-0.37, 1.20]
2	SC	0.30	[-0.28, 0.88]
2	SC + ST	0.35	[-0.19, 0.89]
2	ST	0.47	[-0.09, 1.02]
3_A	Combi_CBT	0.38	[-0.05, 0.81]
3_A	Single_CBT	0.33	[-0.26, 0.93]
3_B	Combi_HA	0.43	[-0.08, 0.94]
3_B	Single_HA	0.35	[-0.16, 0.87]
3_C	Combi_SC	0.30	[-0.08, 0.68]
3_C	Single_SC	0.30	[-0.29, 0.89]
3_D	Combi_ST	0.36	[-0.01, 0.73]
3_D	Single_ST	0.47	[-0.10, 1.04]
4_A	Doesnt_have_CBT	0.36	[0.11, 0.61]
4_A	Has_CBT	0.36	[0.02, 0.70]
4_B	Doesnt_have_HA	0.34	[-0.09, 0.76]
4_B	Has_HA	0.39	[0.03, 0.75]
4_C	Doesnt_have_SC	0.40	[0.14, 0.66]
4_C	Has_SC	0.30	[-0.02, 0.61]
4_D	Doesnt_have_ST	0.34	[0.06, 0.61]
4_D	Has_ST	0.39	[0.09, 0.70]
5	Brain	0.31	[-0.05, 0.66]
5	Brain_and_Ear	0.37	[0.01, 0.73]
5	Ear	0.41	[0.06, 0.75]

Note. Values depict least-squares mean changes with 95% CI in square brackets. Objective 1: Single vs. Combination (all treatments); Objective 2: All treatments against each other; Objective 3: Single vs. Combination (separately); Objective 4: Treatments with vs. treatments without; Objective 5: Ear-mediated vs. brain-mediated vs. ear- and brain-mediated treatments. CBT = Cognitive-Behavioural Therapy; HA = Hearing Aids; SC = Structured Counselling; ST = Sound Therapy.

26. Table S21: Secondary Outcome (WHO-QoL-Bref 3: Social Factors) at Final Visit

Objective	Contrast	Change from baseline	95% CI
1	Combination	0.17	[-0.26, 0.60]
1	Single	0.20	[-0.22, 0.63]
2	CBT	0.26	[-0.62, 1.14]
2	CBT + HA	0.49	[-1.14, 2.12]
2	CBT + SC	0.62	[-0.35, 1.59]
2	CBT + ST	0.14	[-0.76, 1.04]
2	HA	0.63	[-0.18, 1.43]
2	HA + SC	0.93	[-0.48, 2.34]
2	HA + ST	-0.09	[-1.27, 1.10]
2	SC	0.01	[-0.86, 0.88]
2	SC + ST	-0.38	[-1.19, 0.42]
2	ST	-0.09	[-0.93, 0.75]
3_A	Combi_CBT	0.39	[-0.23, 1.01]
3_A	Single_CBT	0.26	[-0.62, 1.14]
3_B	Combi_HA	0.38	[-0.40, 1.15]
3_B	Single_HA	0.63	[-0.16, 1.41]
3_C	Combi_SC	0.19	[-0.35, 0.73]
3_C	Single_SC	0.01	[-0.82, 0.84]
3_D	Combi_ST	-0.13	[-0.69, 0.43]
3_D	Single_ST	-0.09	[-0.97, 0.79]
4_A	Doesnt_have_CBT	0.08	[-0.31, 0.47]
4_A	Has_CBT	0.35	[-0.16, 0.86]
4_B	Doesnt_have_HA	0.30	[-0.34, 0.94]
4_B	Has_HA	0.50	[-0.07, 1.06]
4_C	Doesnt_have_SC	0.22	[-0.18, 0.62]
4_C	Has_SC	0.14	[-0.35, 0.62]
4_D	Doesnt_have_ST	0.43	[0.01, 0.84]
4_D	Has_ST	-0.12	[-0.58, 0.34]
5	Brain	0.29	[-0.24, 0.81]
5	Brain_and_Ear	0.06	[-0.47, 0.59]
5	Ear	0.20	[-0.32, 0.73]

Note. Values depict least-squares mean changes with 95% CI in square brackets. Objective 1: Single vs. Combination (all treatments); Objective 2: All treatments against each other; Objective 3: Single vs. Combination (separately); Objective 4: Treatments with vs. treatments without; Objective 5: Ear-mediated vs. brain-mediated vs. ear- and brain-mediated treatments. CBT = Cognitive-Behavioural Therapy; HA = Hearing Aids; SC = Structured Counselling; ST = Sound Therapy.

27. Table S22: Secondary Outcome (WHO-QoL-Bref 4: Environment) at Final Visit

Objective	Contrast	Change from baseline	95% CI
1	Combination	0.28	[-0.04, 0.61]
1	Single	0.35	[0.02, 0.67]
2	CBT	0.36	[-0.31, 1.02]
2	CBT + HA	0.57	[-0.72, 1.85]
2	CBT + SC	0.06	[-0.64, 0.75]
2	CBT + ST	0.46	[-0.21, 1.13]
2	HA	0.74	[0.14, 1.34]
2	HA + SC	0.66	[-0.44, 1.75]
2	HA + ST	0.35	[-0.53, 1.23]
2	SC	0.11	[-0.54, 0.76]
2	SC + ST	0.09	[-0.52, 0.71]
2	ST	0.17	[-0.47, 0.80]
3_A	Combi_CBT	0.31	[-0.13, 0.74]
3_A	Single_CBT	0.36	[-0.28, 0.99]
3_B	Combi_HA	0.50	[-0.11, 1.11]
3_B	Single_HA	0.74	[0.15, 1.33]
3_C	Combi_SC	0.16	[-0.27, 0.59]
3_C	Single_SC	0.11	[-0.56, 0.78]
3_D	Combi_ST	0.28	[-0.13, 0.69]
3_D	Single_ST	0.17	[-0.47, 0.81]
4_A	Doesnt_have_CBT	0.31	[0.02, 0.60]
4_A	Has_CBT	0.32	[-0.06, 0.71]
4_B	Doesnt_have_HA	0.29	[-0.20, 0.77]
4_B	Has_HA	0.62	[0.21, 1.02]
4_C	Doesnt_have_SC	0.43	[0.13, 0.73]
4_C	Has_SC	0.14	[-0.21, 0.50]
4_D	Doesnt_have_ST	0.37	[0.06, 0.67]
4_D	Has_ST	0.25	[-0.10, 0.59]
5	Brain	0.18	[-0.21, 0.57]
5	Brain_and_Ear	0.35	[-0.06, 0.75]
5	Ear	0.44	[0.04, 0.83]

Note. Values depict least-squares mean changes with 95% CI in square brackets. Objective 1: Single vs. Combination (all treatments); Objective 2: All treatments against each other; Objective 3: Single vs. Combination (separately); Objective 4: Treatments with vs. treatments without; Objective 5: Ear-mediated vs. brain-mediated vs. ear- and brain-mediated treatments. CBT = Cognitive-Behavioural Therapy; HA = Hearing Aids; SC = Structured Counselling; ST = Sound Therapy.

28. *Table S23: Secondary Outcome (NRS 1: "How much of a problem is your tinnitus at present?") at Final Visit*

Objective	Contrast	Change from baseline	95% CI
1	Combination	-0.53	[-0.71, -0.35]
1	Single	-0.49	[-0.67, -0.31]
2	CBT	-0.53	[-0.94, -0.11]
2	CBT + HA	-0.87	[-1.55, -0.20]
2	CBT + SC	-0.54	[-0.93, -0.14]
2	CBT + ST	-0.57	[-0.95, -0.19]
2	HA	-0.60	[-0.94, -0.27]
2	HA + SC	-0.49	[-1.09, 0.11]
2	HA + ST	-0.58	[-1.07, -0.08]
2	SC	-0.61	[-0.98, -0.25]
2	SC + ST	-0.39	[-0.72, -0.05]
2	ST	-0.24	[-0.60, 0.12]
3_A	Combi_CBT	-0.60	[-0.86, -0.33]
3_A	Single_CBT	-0.53	[-0.96, -0.09]
3_B	Combi_HA	-0.63	[-0.95, -0.31]
3_B	Single_HA	-0.60	[-0.91, -0.29]
3_C	Combi_SC	-0.46	[-0.69, -0.23]
3_C	Single_SC	-0.61	[-0.96, -0.27]
3_D	Combi_ST	-0.49	[-0.72, -0.26]
3_D	Single_ST	-0.24	[-0.61, 0.13]
4_A	Doesnt_have_CBT	-0.47	[-0.63, -0.31]
4_A	Has_CBT	-0.58	[-0.79, -0.36]
4_B	Doesnt_have_HA	-0.38	[-0.65, -0.12]
4_B	Has_HA	-0.62	[-0.85, -0.39]
4_C	Doesnt_have_SC	-0.52	[-0.69, -0.35]
4_C	Has_SC	-0.50	[-0.71, -0.30]
4_D	Doesnt_have_ST	-0.58	[-0.75, -0.41]
4_D	Has_ST	-0.42	[-0.61, -0.23]
5	Brain	-0.56	[-0.78, -0.34]
5	Brain_and_Ear	-0.52	[-0.74, -0.30]
5	Ear	-0.45	[-0.67, -0.23]

Note. Values depict least-squares mean changes with 95% CI in square brackets. Since the outcome is ordinally scaled, it was fitted as a sensitivity analysis with clmm of the ordinal package, as no differences were found to the mixed effect model, the results of the mixed effect model are reported here. Objective 1: Single vs. Combination (all treatments); Objective 2: All treatments against each other; Objective 3: Single vs. Combination (separately); Objective 4: Treatments with vs. treatments without; Objective 5: Ear-mediated vs. brain-mediated vs. ear-and brain-mediated treatments. CBT = Cognitive-Behavioural Therapy; HA = Hearing Aids; SC = Structured Counselling; ST = Sound Therapy.

29. *Table S24: Secondary Outcome (NRS 3: "How uncomfortable is your tinnitus at present?") at Final Visit*

Objective	Contrast	Change from baseline	95% CI
1	Combination	-1.68	[-2.13, -1.23]
1	Single	-1.25	[-1.70, -0.80]
2	CBT	-1.76	[-2.72, -0.80]
2	CBT + HA	-1.94	[-3.71, -0.17]
2	CBT + SC	-1.94	[-2.94, -0.93]
2	CBT + ST	-1.68	[-2.65, -0.72]
2	HA	-1.63	[-2.50, -0.77]
2	HA + SC	-1.22	[-2.76, 0.32]
2	HA + ST	-1.65	[-2.92, -0.38]
2	SC	-1.08	[-2.00, -0.16]
2	SC + ST	-1.55	[-2.42, -0.68]
2	ST	-0.55	[-1.44, 0.33]
3_A	Combi_CBT	-1.83	[-2.47, -1.18]
3_A	Single_CBT	-1.76	[-2.72, -0.80]
3_B	Combi_HA	-1.60	[-2.49, -0.71]
3_B	Single_HA	-1.63	[-2.52, -0.75]
3_C	Combi_SC	-1.65	[-2.25, -1.05]
3_C	Single_SC	-1.08	[-2.01, -0.15]
3_D	Combi_ST	-1.62	[-2.20, -1.03]
3_D	Single_ST	-0.55	[-1.45, 0.34]
4_A	Doesnt_have_CBT	-1.25	[-1.66, -0.85]
4_A	Has_CBT	-1.80	[-2.34, -1.27]
4_B	Doesnt_have_HA	-1.14	[-1.80, -0.47]
4_B	Has_HA	-1.62	[-2.22, -1.01]
4_C	Doesnt_have_SC	-1.46	[-1.87, -1.04]
4_C	Has_SC	-1.48	[-1.98, -0.98]
4_D	Doesnt_have_ST	-1.59	[-2.02, -1.16]
4_D	Has_ST	-1.31	[-1.80, -0.82]
5	Brain	-1.58	[-2.14, -1.02]
5	Brain_and_Ear	-1.60	[-2.16, -1.04]
5	Ear	-1.20	[-1.75, -0.64]

Note. Values depict least-squares mean changes with 95% CI in square brackets. Objective 1: Single vs. Combination (all treatments); Objective 2: All treatments against each other; Objective 3: Single vs. Combination (separately); Objective 4: Treatments with vs. treatments without; Objective 5: Ear-mediated vs. brain-mediated vs. ear- and brain-mediated treatments. CBT = Cognitive-Behavioural Therapy; HA = Hearing Aids; SC = Structured Counselling; ST = Sound Therapy.

30. Table S25: Secondary outcome (NRS 4: "How annoying is your tinnitus at present?") at Final Visit

Objective	Contrast	Change from baseline	95% CI
1	Combination	-1.53	[-1.99, -1.08]
1	Single	-1.18	[-1.62, -0.73]
2	CBT	-1.58	[-2.55, -0.62]
2	CBT + HA	-2.00	[-3.73, -0.27]
2	CBT + SC	-1.83	[-2.84, -0.81]
2	CBT + ST	-1.29	[-2.23, -0.36]
2	HA	-1.63	[-2.49, -0.78]
2	HA + SC	-1.68	[-3.21, -0.16]
2	HA + ST	-1.16	[-2.42, 0.09]
2	SC	-1.03	[-1.97, -0.10]
2	SC + ST	-1.48	[-2.34, -0.63]
2	ST	-0.47	[-1.35, 0.42]
3_A	Combi_CBT	-1.61	[-2.26, -0.97]
3_A	Single_CBT	-1.58	[-2.55, -0.62]
3_B	Combi_HA	-1.55	[-2.43, -0.66]
3_B	Single_HA	-1.63	[-2.53, -0.73]
3_C	Combi_SC	-1.64	[-2.24, -1.04]
3_C	Single_SC	-1.03	[-1.96, -0.10]
3_D	Combi_ST	-1.35	[-1.93, -0.78]
3_D	Single_ST	-0.47	[-1.36, 0.43]
4_A	Doesnt_have_CBT	-1.20	[-1.61, -0.78]
4_A	Has_CBT	-1.60	[-2.13, -1.08]
4_B	Doesnt_have_HA	-1.14	[-1.81, -0.46]
4_B	Has_HA	-1.59	[-2.19, -0.98]
4_C	Doesnt_have_SC	-1.28	[-1.69, -0.87]
4_C	Has_SC	-1.46	[-1.98, -0.94]
4_D	Doesnt_have_ST	-1.56	[-1.99, -1.13]
4_D	Has_ST	-1.09	[-1.58, -0.61]
5	Brain	-1.47	[-2.02, -0.92]
5	Brain_and_Ear	-1.50	[-2.05, -0.94]
5	Ear	-1.07	[-1.62, -0.52]

Note. Values depict least-squares mean changes with 95% CI in square brackets. Objective 1: Single vs. Combination (all treatments); Objective 2: All treatments against each other; Objective 3: Single vs. Combination (separately); Objective 4: Treatments with vs. treatments without; Objective 5: Ear-mediated vs. brain-mediated vs. ear- and brain-mediated treatments. CBT = Cognitive-Behavioural Therapy; HA = Hearing Aids; SC = Structured Counselling; ST = Sound Therapy.

31. *Table S26: Secondary outcome (NRS 5: "How easy is it for you to ignore your tinnitus at present?") at Final Visit*

Objective	Contrast	Change from baseline	95% CI
1	Combination	-1.71	[-2.26, -1.16]
1	Single	-1.20	[-1.74, -0.66]
2	CBT	-1.67	[-2.82, -0.52]
2	CBT + HA	-2.41	[-4.51, -0.30]
2	CBT + SC	-1.92	[-3.12, -0.73]
2	CBT + ST	-1.75	[-2.88, -0.63]
2	HA	-1.29	[-2.33, -0.25]
2	HA + SC	-0.87	[-2.73, 0.98]
2	HA + ST	-2.18	[-3.69, -0.66]
2	SC	-1.18	[-2.27, -0.10]
2	SC + ST	-1.36	[-2.39, -0.32]
2	ST	-0.68	[-1.72, 0.36]
3_A	Combi_CBT	-1.92	[-2.71, -1.12]
3_A	Single_CBT	-1.67	[-2.84, -0.50]
3_B	Combi_HA	-1.85	[-2.88, -0.81]
3_B	Single_HA	-1.29	[-2.33, -0.25]
3_C	Combi_SC	-1.50	[-2.22, -0.79]
3_C	Single_SC	-1.18	[-2.26, -0.11]
3_D	Combi_ST	-1.66	[-2.35, -0.97]
3_D	Single_ST	-0.68	[-1.75, 0.39]
4_A	Doesnt_have_CBT	-1.21	[-1.69, -0.74]
4_A	Has_CBT	-1.84	[-2.49, -1.19]
4_B	Doesnt_have_HA	-0.95	[-1.73, -0.16]
4_B	Has_HA	-1.58	[-2.29, -0.87]
4_C	Doesnt_have_SC	-1.49	[-1.99, -0.99]
4_C	Has_SC	-1.41	[-2.01, -0.80]
4_D	Doesnt_have_ST	-1.52	[-2.05, -0.99]
4_D	Has_ST	-1.37	[-1.94, -0.81]
5	Brain	-1.58	[-2.26, -0.90]
5	Brain_and_Ear	-1.55	[-2.22, -0.88]
5	Ear	-1.21	[-1.87, -0.55]

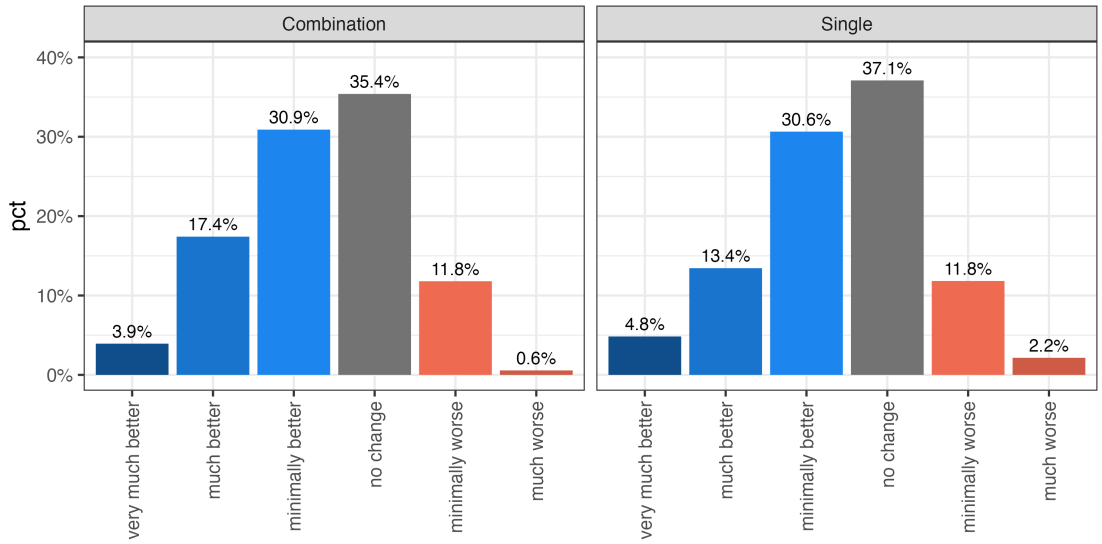
Note. Values depict least-squares mean changes with 95% CI in square brackets. Objective 1: Single vs. Combination (all treatments); Objective 2: All treatments against each other; Objective 3: Single vs. Combination (separately); Objective 4: Treatments with vs. treatments without; Objective 5: Ear-mediated vs. brain-mediated vs. ear- and brain-mediated treatments. CBT = Cognitive-Behavioural Therapy; HA = Hearing Aids; SC = Structured Counselling; ST = Sound Therapy.

32. Table S27: Secondary outcome (NRS 6: "How unpleasant is your tinnitus at present?") at Final Visit

Objective	Contrast	Change from baseline	95% CI
1	Combination	-1.37	[-1.83, -0.91]
1	Single	-1.16	[-1.61, -0.71]
2	CBT	-1.31	[-2.31, -0.31]
2	CBT + HA	-1.93	[-3.64, -0.23]
2	CBT + SC	-1.93	[-2.90, -0.97]
2	CBT + ST	-1.11	[-2.06, -0.16]
2	HA	-1.40	[-2.24, -0.55]
2	HA + SC	-1.32	[-2.81, 0.16]
2	HA + ST	-1.38	[-2.61, -0.15]
2	SC	-1.14	[-2.05, -0.24]
2	SC + ST	-1.00	[-1.83, -0.16]
2	ST	-0.80	[-1.65, 0.05]
3_A	Combi_CBT	-1.57	[-2.22, -0.92]
3_A	Single_CBT	-1.31	[-2.31, -0.31]
3_B	Combi_HA	-1.51	[-2.39, -0.64]
3_B	Single_HA	-1.40	[-2.29, -0.50]
3_C	Combi_SC	-1.40	[-1.98, -0.82]
3_C	Single_SC	-1.14	[-2.04, -0.25]
3_D	Combi_ST	-1.11	[-1.70, -0.52]
3_D	Single_ST	-0.80	[-1.67, 0.07]
4_A	Doesnt_have_CBT	-1.13	[-1.52, -0.73]
4_A	Has_CBT	-1.49	[-2.03, -0.95]
4_B	Doesnt_have_HA	-1.01	[-1.67, -0.36]
4_B	Has_HA	-1.46	[-2.05, -0.86]
4_C	Doesnt_have_SC	-1.22	[-1.64, -0.81]
4_C	Has_SC	-1.33	[-1.82, -0.83]
4_D	Doesnt_have_ST	-1.46	[-1.89, -1.03]
4_D	Has_ST	-1.02	[-1.49, -0.55]
5	Brain	-1.45	[-2.01, -0.89]
5	Brain_and_Ear	-1.18	[-1.74, -0.62]
5	Ear	-1.15	[-1.69, -0.61]

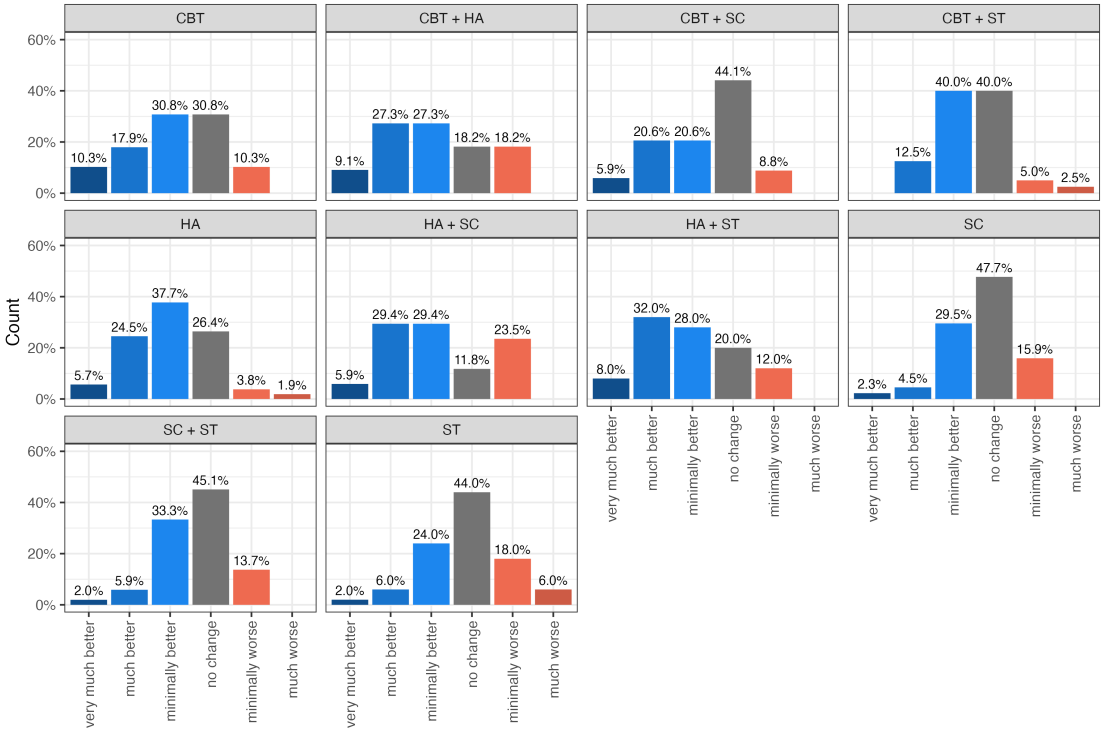
Note. Values depict least-squares mean changes with 95% CI in square brackets. Objective 1: Single vs. Combination (all treatments); Objective 2: All treatments against each other; Objective 3: Single vs. Combination (separately); Objective 4: Treatments with vs. treatments without; Objective 5: Ear-mediated vs. brain-mediated vs. ear- and brain-mediated treatments. CBT = Cognitive-Behavioural Therapy; HA = Hearing Aids; SC = Structured Counselling; ST = Sound Therapy.

33. *Figure S6: Secondary Outcome (CGI-I) at Final Visit – Single vs. Combination (Objective 1)*



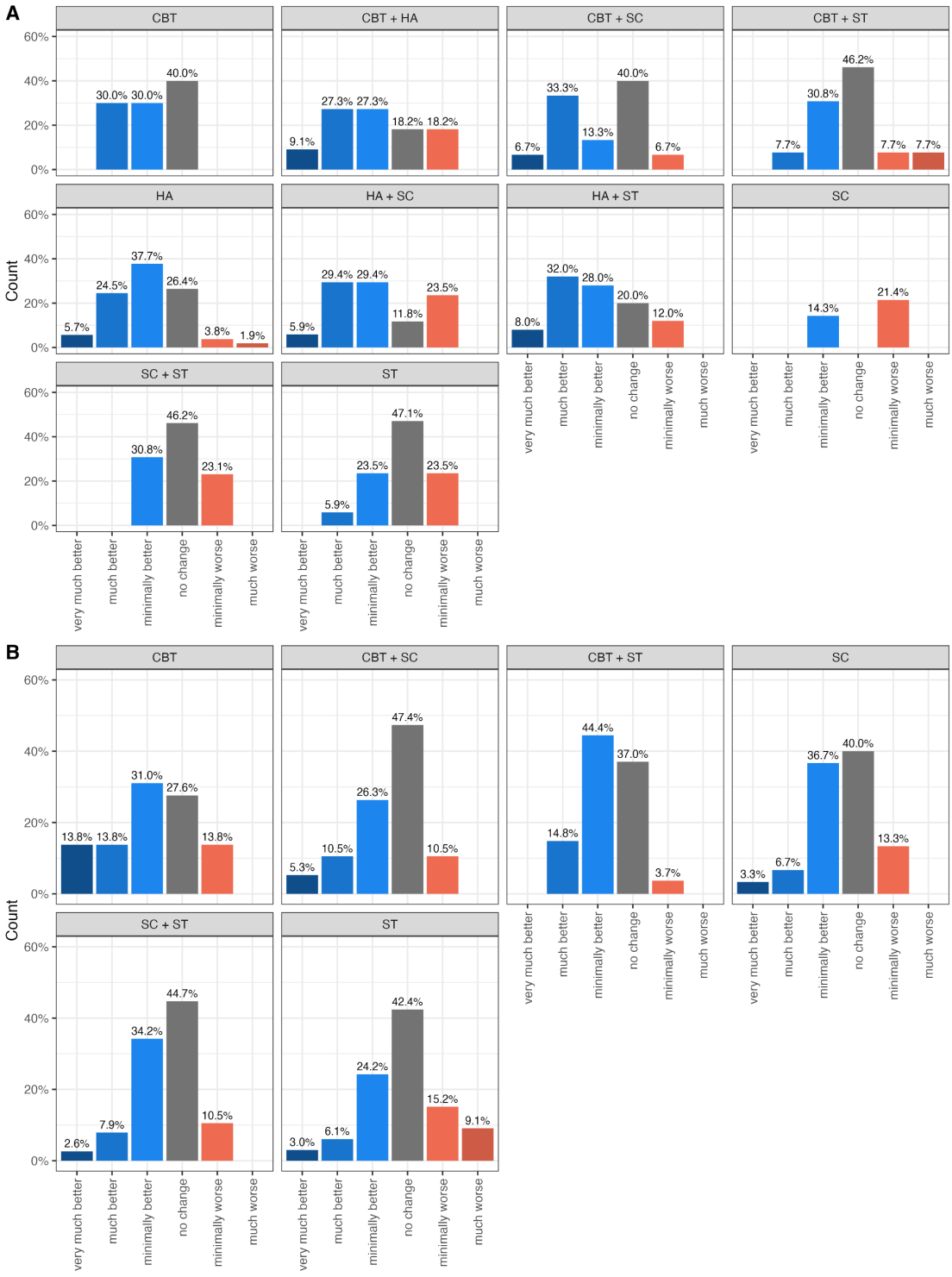
Note. Distribution (in percentage) of CGI-I (Clinical Global Impression Scale) at final visit for Objective 1.

34. *Figure S7: Secondary Outcome (CGI-I) at Final Visit – all Treatment Arms (Objective 2)*



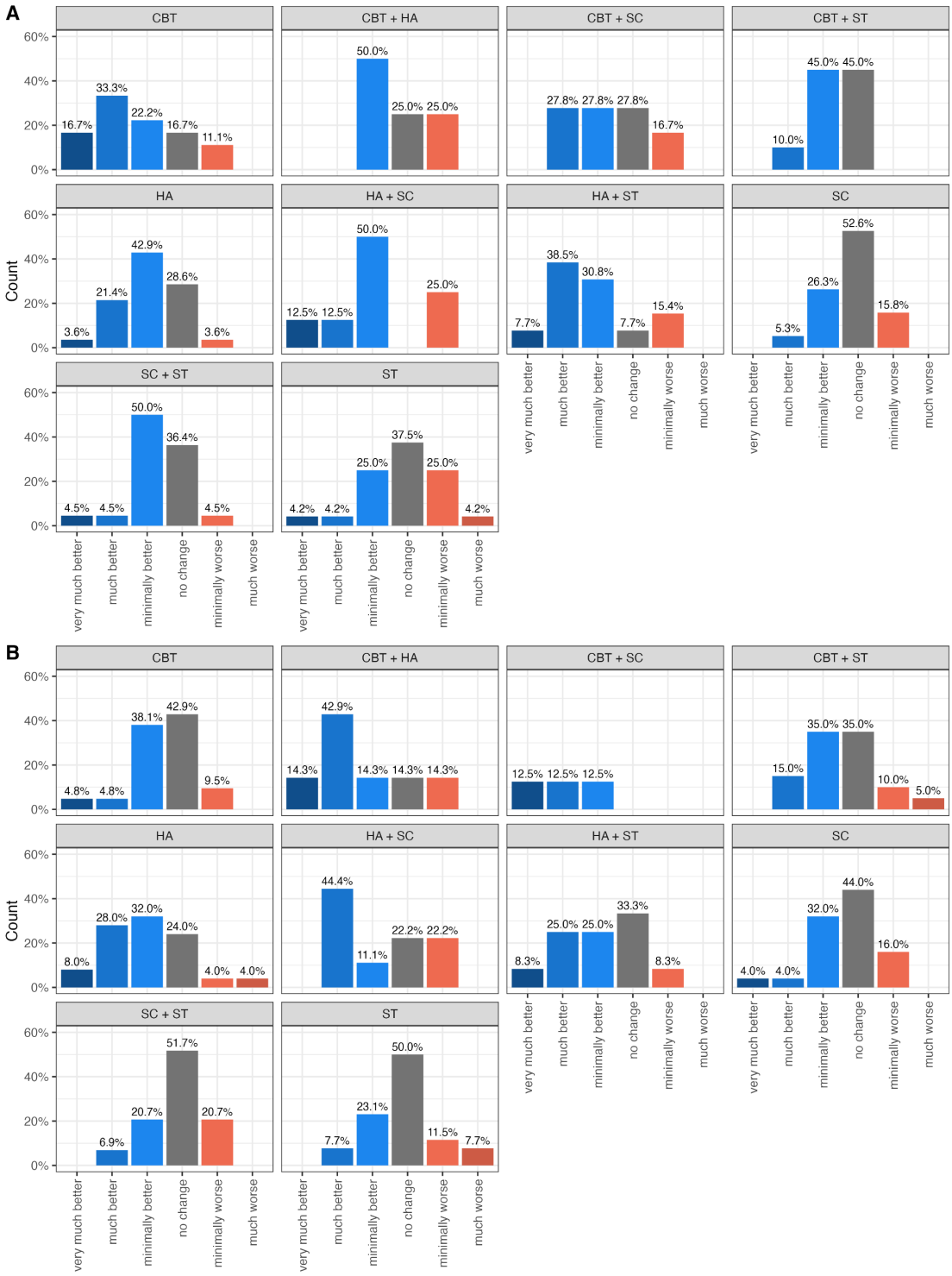
Note. Distribution (in percentage) of CGI-I (Clinical Global Impression Scale) at final visit for Objective 2. CBT = Cognitive-Behavioural Therapy; HA = Hearing Aids; SC = Structured Counselling; ST = Sound Therapy.

35. *Figure S8: Secondary Outcome (CGI-I) at Final Visit – all Treatment Arms (Objective 2) in Patients With and Without Hearing Aid Indication*



Note. Distribution (in percentage) of CGI-I (Clinical Global Impression Scale) at final visit for Objective 2 in patients (A) with hearing aid indication and (B) without hearing aid indication. CBT = Cognitive-Behavioural Therapy; HA = Hearing Aids; SC = Structured Counselling; ST = Sound Therapy.

36. *Figure S9: Secondary Outcome (CGI-I) at Final Visit – all Treatment Arms (Objective 2) in Patients with High and Low Tinnitus Distress Severity*



Note. Distribution (in percentage) of CGI-I (Clinical Global Impression Scale) at final visit for Objective 2 in patients (A) with High and (B) Low tinnitus distress severity. High tinnitus distress severity: THI ≥ 48 at Screening. Low tinnitus distress severity: THI < 48 at Screening. CBT = Cognitive-Behavioural Therapy; HA = Hearing Aids; SC = Structured Counselling; ST = Sound Therapy.

37. Table S28: Quantity and Type of Adverse Events per Treatment Arm

Treatment arm	*Adverse event*	*Treatment arm*	*Adverse event*
CBT	Reconstruction nasal septum	***CBT + HA***	Herpes zoster (thigh)
(n = 13)	Thoracic strain	***(n = 5)***	Skin Excision
	Additional burden due to husband's temporary absence		Mental breakdown
	Cold		Invasion Russia
	Diverticulitis disease		Ear pain due to hearing aids
	Torn tendon on the foot	***CBT + SC***	Vaccine reaction (Moderna)
	Sickness of spouse	***(n = 12)***	Lithotripsy
	Toothache		Total endoprosthesis hip
	Cold (suspected Covid-19 positive)		Leukoplakia vocal cord (surgery)
	Gastrointestinal infection		Chronic Fatigue Syndrome
	Worsening general health status		Vaccination reaction
	Death of close friend		Death of the cat, depressive symptoms of the significant other
	Worries about pet		Severe health problems of partner
HA	Mole removal		Angina
(n = 10)	Acute Urine Retention		Death of pet
	Tinnitus worsening		Heavy cold
	Retinal tear		Inheritance dispute with siblings
	Disease of the mother-in-law	***CBT + ST***	Common cold
	Loss of mother-in-law	***(n = 13)***	Covid-19 infection
	Urinary tract infection		Acute pain testis (left)
	Sleep problems		Covid-19 infection
	Covid-19 infection		Bereavement in the family
	Covid-19 infection		Cold
SC	Thyroid nodule (benign)		Mild temporary hearing loss
(n = 11)	Aggravation of tinnitus		Dizziness
	Diverticulitis		Worsening psychological health due to irritable colon or depression
	Tooth extraction		Sleep rhythm disturbed
	Septoplasty		Invasion Russia
	Stye		Covid-19 infection
	Professional reorientation		Tinnitus worsening
	Parents-in-law's dementia exacerbation	***HA + SC***	Broken foot
	Bicycle accident	***(n = 3)***	Ear infection due to hearing aid

	Additional task at work		Toothache
	Shoulder pain	***HA + ST***	Inflammation of the ear
ST	Surgery hand (plate removal)	***(n = 5)***	Frozen Shoulder
(n = 15)	Burglary		Travel problem on Airport
	Bicycle accident		Severe cold
	Influenza		Work stress
	Vaccine reaction (Covid-19)	***SC + ST***	Lymph node removal (groin)
	Depression	***(n = 11)***	Forthcoming divorce
	Tooth infection and extraction		A lot of stress at the beginning of the school year
	Great workload and stress		Covid-19 infection
	Sprained foot		Migraine
	Disastrous vacation		Tinnitus worsening
	Cold		Tinnitus worsening
	Cold		Accident
	Persistent tiredness		Stress at work
	Gastrointestinal infection		Bicycle accident
	Tinnitus unchanged but more present and therefore more bothersome		Conflict with spouse

Note. Adverse events potentially associated with treatment were worsening of the tinnitus percept (6); worsening of psychological health (3); sleep problems (2); pain in the ear when wearing the hearing aid (1), ear infection (1), inflammation of the ear (1), dizziness (1), and mild transient hearing loss (1). CBT = Cognitive-Behavioural Therapy; HA = Hearing Aids; SC = Structured Counselling; ST = Sound Therapy.

38. Table S29: Compliance to Treatments

	CBT	**HA – left**	**HA – right**	**SC**	**ST**
Mean	7.5	5.0	5.3	47.1	108.6
Sd	3.7	3.1	3.3	32.0	149.9

Note. CBT (Cognitive Behavioural Therapy): number of CBT sessions attended. HA (hearing aids) – left: average daily wearing time of hearing aids left (in hours). HA – right: average daily wearing time of hearing aids right (in hours). SC (Structured Counseling): number of completed SC sections. ST (Sound Therapy): number of sounds played in ST.

39. Table S30: Primary Outcome (THI) Objective 2: Post-hoc Comparisons (Baseline to Final Visit)

Contrast (baseline – final visit)	Estimate	95% CI	p	p-adjusted
CBT - (CBT + HA)	1.62	[-7.47, 10.71]	.727	1.00
CBT - (CBT + SC)	-0.53	[-7.01, 5.96]	.874	1.00
CBT - (CBT + ST)	2.77	[-3.56, 9.11]	.391	1.00
CBT - HA	2.46	[-3.50, 8.42]	.419	1.00
CBT - (HA + SC)	-3.18	[-11.50, 5.15]	.454	1.00
CBT - (HA + ST)	3.93	[-3.43, 11.29]	.295	1.00
CBT - SC	4.86	[-1.26, 10.98]	.119	1.00
CBT - (SC + ST)	4.21	[-1.70, 10.11]	.162	1.00
CBT - ST	13.03	[6.85, 19.21]	< .001***	< .001***
(CBT + HA) - (CBT + SC)	-2.14	[-11.60, 7.31]	.656	1.00
(CBT + HA) - (CBT + ST)	1.16	[-8.30, 10.61]	.811	1.00
(CBT + HA) - HA	0.84	[-8.24, 9.92]	.856	1.00
(CBT + HA) - (HA + SC)	-4.80	[-15.57, 5.98]	.383	1.00
(CBT + HA) - (HA + ST)	2.31	[-7.81, 12.43]	.654	1.00
(CBT + HA) - SC	3.24	[-5.97, 12.45]	.490	1.00
(CBT + HA) - (SC + ST)	2.59	[-6.56, 11.74]	.579	1.00
(CBT + HA) - ST	11.41	[2.21, 20.62]	.015*	.675
(CBT + SC) - (CBT + ST)	3.30	[-3.38, 9.98]	.333	1.00
(CBT + SC) - HA	2.98	[-3.30, 9.26]	.352	1.00
(CBT + SC) - (HA + SC)	-2.65	[-11.13, 5.83]	.540	1.00
(CBT + SC) - (HA + ST)	4.46	[-3.02, 11.93]	.242	1.00
(CBT + SC) - SC	5.39	[-1.05, 11.83]	.101	1.00
(CBT + SC) - (SC + ST)	4.73	[-1.43, 10.90]	.132	1.00
(CBT + SC) - ST	13.56	[7.21, 19.90]	< .001***	< .001***
(CBT + ST) - HA	-0.32	[-6.22, 5.59]	.916	1.00
(CBT + ST) - (HA + SC)	-5.95	[-14.30, 2.40]	.162	1.00
(CBT + ST) - (HA + ST)	1.16	[-6.07, 8.38]	.753	1.00
(CBT + ST) - SC	2.09	[-3.94, 8.11]	.497	1.00
(CBT + ST) - (SC + ST)	1.43	[-4.47, 7.34]	.634	1.00
(CBT + ST) - ST	10.26	[4.32, 16.19]	.001**	.045*
HA - (HA + SC)	-5.63	[-13.75, 2.48]	.173	1.00
HA - (HA + ST)	1.48	[-5.56, 8.51]	.681	1.00

Contrast (baseline – final visit)	Estimate	95% CI	p	p-adjusted
HA - SC	2.40	[-3.36, 8.17]	.413	1.00
HA - (SC + ST)	1.75	[-3.84, 7.34]	.539	1.00
HA - ST	10.57	[4.78, 16.37]	< .001***	< .001***
(HA + SC) - (HA + ST)	7.11	[-2.05, 16.27]	.128	1.00
(HA + SC) - SC	8.04	[-0.09, 16.16]	.053	1.00
(HA + SC) - (SC + ST)	7.38	[-0.65, 15.42]	.072	1.00
(HA + SC) - ST	16.21	[8.06, 24.36]	< .001***	< .001***
(HA + ST) - SC	0.93	[-6.23, 8.09]	.799	1.00
(HA + ST) - (SC + ST)	0.28	[-6.75, 7.30]	.939	1.00
(HA + ST) - ST	9.10	[2.03, 16.16]	.012*	.540
SC - (SC + ST)	-0.65	[-6.39, 5.08]	.823	1.00
SC - ST	8.17	[2.29, 14.05]	.006**	.270
(SC + ST) - ST	8.82	[3.20, 14.45]	.002**	.090

Note. Objective 2: Pairwise comparison of treatments for the THI difference from baseline to final visit (post-hoc tests). The comparisons are based on a linear mixed effects model predicting the primary outcome by objective, time point (baseline, interim visit, final visit, and follow-up), and objective-by-time interaction as fixed effects, including centre and subject ID as random intercepts. The model was adjusted for the following covariates: age, sex, educational attainment, hearing aid indication, and PHQ-9 baseline scores. All comparisons are two-sided and p-values were adjusted for multiple comparisons using the Bonferroni method. CBT = Cognitive-Behavioural Therapy; HA = Hearing Aids; SC = Structured Counselling; ST = Sound Therapy. *p<0.05, **p<0.01, ***p<0.001.

40. Table S31: Sensitivity Analysis - Primary Outcome (THI) at Final Visit

Objective	Contrast	Change from baseline	95% CI
1	Combination	-15.10	[-17.96, -12.24]
1	Single	-11.53	[-14.34, -8.72]
2	CBT	-18.12	[-24.10, -12.14]
2	CBT + HA	-16.00	[-27.17, -4.82]
2	CBT + SC	-19.17	[-25.55, -12.79]
2	CBT + ST	-14.02	[-19.96, -8.08]
2	HA	-14.50	[-19.74, -9.27]
2	HA + SC	-20.67	[-29.92, -11.42]
2	HA + ST	-12.92	[-20.59, -5.25]
2	SC	-11.66	[-17.35, -5.97]
2	SC + ST	-12.48	[-17.77, -7.19]
2	ST	-3.03	[-8.39, 2.33]
3_A	Combi_CBT	-16.36	[-20.49, -12.23]
3_A	Single_CBT	-18.31	[-24.41, -12.21]
3_B	Combi_HA	-15.98	[-20.92, -11.04]
3_B	Single_HA	-14.54	[-19.50, -9.58]
3_C	Combi_SC	-16.02	[-19.74, -12.30]
3_C	Single_SC	-11.66	[-17.35, -5.96]
3_D	Combi_ST	-13.05	[-16.66, -9.44]
3_D	Single_ST	-3.01	[-8.52, 2.51]
4_A	Doesnt_have_CBT	-11.40	[-13.90, -9.00]
4_A	Has_CBT	-16.90	[-20.30, -13.50]
4_B	Doesnt_have_HA	-11.09	[-15.19, -7.00]
4_B	Has_HA	-15.27	[-18.92, -11.61]
4_C	Doesnt_have_SC	-12.31	[-14.91, -9.71]
4_C	Has_SC	-14.70	[-17.87, -11.54]
4_D	Doesnt_have_ST	-15.97	[-18.68, -13.27]
4_D	Has_ST	-10.06	[-13.02, -7.09]
5	Brain	-16.00	[-19.49, -12.50]
5	Brain_and_Ear	-14.43	[-17.92, -10.94]
5	Ear	-9.69	[-13.09, -6.29]

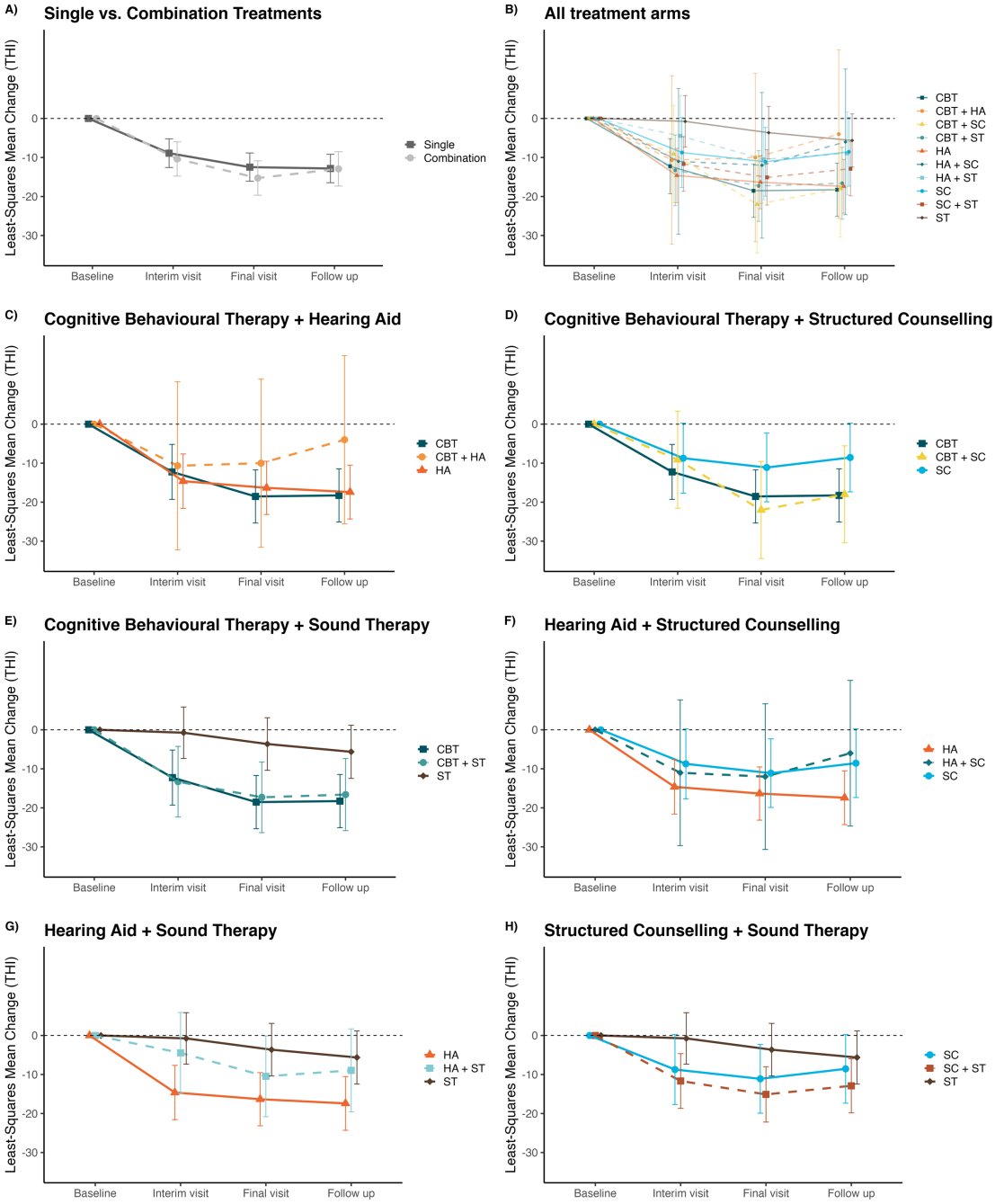
Note. Values depict least-squares mean changes with 95% CI in square brackets. Sensitivity analysis for the primary outcome was performed without imputation of the primary outcome. Objective 1: Single vs. Combination (all treatments); Objective 2: All treatments against each other; Objective 3: Single vs. Combination (separately); Objective 4: Treatments with vs. treatments without; Objective 5: Ear-mediated vs. brain-mediated vs. ear- and brain-mediated treatments. CBT = Cognitive-Behavioural Therapy; HA = Hearing Aids; SC = Structured Counselling; ST = Sound Therapy.

41. Table S32: Sensitivity Analysis – Robustness Check of the Primary Outcome (THI) at Final Visit using different Imputation Methods

Imputation method	Least-square mean change – single	Least-square mean change – combination	ß estimate	p value
Multilevel imputation	-11.7 [-14.4; -9.0]	-14.9 [-17.7; -12.1]	3.2 [0.2; 6.1]	0.034
No imputation	-11.5 [-14.3; -8.7]	-15.1 [-18.0; -12.2]	3.6 [0.5; 6.6]	0.022
Reference-based imputation (J2R)	-12.3 [-15.2; -9.4]	-14.5 [-17.1; -12.0]	2.3 [-1.7; 6.2]	0.252
Reference-based imputation (CIR)	-12.3 [-15.2; -9.4]	-14.5 [-17.2; -11.7]	2.2 [-2.0; 6.4]	0.292
Reference-based imputation (CR)	-12.3 [-15.2; -9.4]	-14.5 [-17.2; -11.8]	2.2 [-1.9; 6.3]	0.281
LOCF	-9.5 [-12.0; -7.1]	-12.6 [-15.1; -10.2]	3.1 [0.4; 5.7]	0.024

Note. Results of the primary objective (THI; single vs. combination treatments) under different assumptions of the missing data mechanism. Depicted are least-square mean changes with 95% CI in square brackets and the results (*ß* estimate with 95% CI in square brackets and *p* value) of the interaction effect (single vs. combination treatments at final visit vs. baseline). Reference-based imputation methods fill missing values following the distribution of a designated reference arm. We used the single treatment arm as reference (R package `RefBasedMI`). *Jump to reference* (J2R): As soon as a participant has a missing value, all future outcomes are set to match the reference arm's trajectory from that point onward. *Copy increments in reference* (CIR): Missing values are imputed by preserving the participant's last observed offset from the reference group but then applying the reference group's subsequent changes. *Copy reference* (CR): Missing values are imputed as if the participant were always in the reference group, effectively discarding any prior difference from the reference. *Last observation carried forward* (LOCF) replaces each participant's missing values with their most recent observed measurement, assuming that the outcome remains unchanged after the last observation (single imputation method).

42. *Figure S10: Per Protocol (N = 185) Primary Outcome (THI)*



Note. Change from Baseline in THI total score to interim visit (6w), final visit (12w) and follow-up (36w) for A) single and combination treatments; B) all treatments; C) CBT + HA; D) CBT + SC; E) CBT + ST; F) HA + SC; G) HA + ST; and H) SC + ST. Total THI scores range from 0 to 100, with higher scores indicating greater severity of tinnitus. Error bars represent 95% confidence intervals.

43. Table S33: Per Protocol (N = 185) Primary Outcome (THI) at Final Visit

Objective	Contrast	Change from baseline	95% CI
1	Combination	-15.27	[-19.68, -10.86]
1	Single	-12.47	[-16.10, -8.84]
2	CBT	-18.53	[-25.35, -11.72]
2	CBT + HA	-10.00	[-31.55, 11.55]
2	CBT + SC	-22.00	[-34.44, -9.56]
2	CBT + ST	-17.29	[-26.35, -8.24]
2	HA	-16.33	[-23.15, -9.52]
2	HA + SC	-12.00	[-30.67, 6.67]
2	HA + ST	-10.46	[-20.82, -0.11]
2	SC	-11.11	[-19.91, -2.31]
2	SC + ST	-15.10	[-22.19, -8.01]
2	ST	-3.64	[-10.38, 3.10]
3_A	Combi_CBT	-18.00	[-25.29, -10.71]
3_A	Single_CBT	-18.53	[-25.70, -11.36]
3_B	Combi_HA	-10.70	[-18.27, -3.13]
3_B	Single_HA	-16.33	[-22.52, -10.15]
3_C	Combi_SC	-16.36	[-22.06, -10.66]
3_C	Single_SC	-11.11	[-19.68, -2.54]
3_D	Combi_ST	-14.70	[-19.71, -9.69]
3_D	Single_ST	-3.63	[-10.51, 3.24]
4_A	Doesnt_have_CBT	-11.38	[-14.75, -8.00]
4_A	Has_CBT	-18.27	[-23.16, -13.38]
4_B	Doesnt_have_HA	-10.84	[-16.53, -5.15]
4_B	Has_HA	-14.08	[-19.28, -8.88]
4_C	Doesnt_have_SC	-13.06	[-16.46, -9.66]
4_C	Has_SC	-14.76	[-19.69, -9.82]
4_D	Doesnt_have_ST	-16.19	[-20.08, -12.31]
4_D	Has_ST	-10.86	[-14.86, -6.86]
5	Brain	-16.74	[-21.73, -11.75]
5	Brain_and_Ear	-15.30	[-20.54, -10.06]
5	Ear	-9.98	[-14.37, -5.59]

Note. Values depict least-squares mean changes with 95% CI in square brackets. Objective 1: Single vs. Combination (all treatments); Objective 2: All treatments against each other; Objective 3: Single vs. Combination (separately); Objective 4: Treatments with vs. treatments without; Objective 5: Ear-mediated vs. brain-mediated vs. ear- and brain-mediated treatments. CBT = Cognitive-Behavioural Therapy; HA = Hearing Aids; SC = Structured Counselling; ST = Sound Therapy.

44. Table S34: Per Protocol 2 (N = 155) Primary Outcome (THI) at Final Visit

Objective	Contrast	Change from baseline	95% CI
1	Combination	-15.49	[-20.31, -10.68]
1	Single	-12.47	[-16.54, -8.40]
2	CBT	-19.05	[-27.26, -10.83]
2	CBT + HA	-10.00	[-31.74, 11.74]
2	CBT + SC	-22.75	[-36.06, -9.44]
2	CBT + ST	-18.29	[-28.35, -8.22]
2	HA	-17.48	[-24.73, -10.23]
2	HA + SC	-15.00	[-41.63, 11.63]
2	HA + ST	-9.64	[-20.99, 1.72]
2	SC	-10.38	[-19.79, -0.96]
2	SC + ST	-14.84	[-22.26, -7.41]
2	ST	-3.07	[-10.55, 4.40]
3_A	Combi_CBT	-18.72	[-26.52, -10.92]
3_A	Single_CBT	-19.05	[-27.56, -10.53]
3_B	Combi_HA	-10.38	[-19.03, -1.72]
3_B	Single_HA	-17.48	[-24.15, -10.82]
3_C	Combi_SC	-16.62	[-22.91, -10.34]
3_C	Single_SC	-10.38	[-19.76, -0.99]
3_D	Combi_ST	-14.66	[-20.15, -9.16]
3_D	Single_ST	-3.05	[-10.82, 4.72]
4_A	Doesnt_have_CBT	-11.52	[-15.20, -7.84]
4_A	Has_CBT	-18.87	[-24.49, -13.25]
4_B	Doesnt_have_HA	-11.03	[-17.36, -4.71]
4_B	Has_HA	-14.84	[-20.60, -9.07]
4_C	Doesnt_have_SC	-13.22	[-17.04, -9.41]
4_C	Has_SC	-14.73	[-20.07, -9.38]
4_D	Doesnt_have_ST	-16.62	[-20.97, -12.28]
4_D	Has_ST	-10.81	[-15.19, -6.44]
5	Brain	-16.62	[-22.33, -10.91]
5	Brain_and_Ear	-15.63	[-21.36, -9.90]
5	Ear	-10.32	[-15.14, -5.51]

Note. Values depict least-squares mean changes with 95% CI in square brackets. Per protocol 2: Additional exclusion of patients where time frame between baseline and final visit exceeded 18 weeks. Objective 1: Single vs. Combination (all treatments); Objective 2: All treatments against each other; Objective 3: Single vs. Combination (separately); Objective 4: Treatments with vs. treatments without; Objective 5: Ear-mediated vs. brain-mediated vs. ear- and brain-mediated treatments. CBT = Cognitive-Behavioural Therapy; HA = Hearing Aids; SC = Structured Counselling; ST = Sound Therapy.

45. Table S35: Clinical Sites and Principal Investigators

Country	**Clinical Site**	**Principal Investigator**
Belgium	Katholieke Universiteit Leuven, Leuven	Asst. Prof. Dr. Rilana Cima Prof. Dr. Johan Vlaeyen
Germany	Tinnitus Center, Charité – Universitatsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin	Prof. Dr. Birgit Mazurek Dr. Benjamin Boecking
	University of Regensburg, Regensburg (RCT coordinator)	Prof. Dr. Berthold Langguth Prof. Dr. Martin Schecklmann PD. Dr. Stefan Schoisswohl
Greece	Ethniko Kai Kapodistriako Panepistimo Athinon, Athens,	PD Dr. Dimitris Kikidis Assoc. Prof. Dr. Athanasios Bibas
Spain	Hospital Universitario Virgen de las Nieves, Granada Hospital Clinico Universitario San Cecilio, Granada	Prof. Dr. Jose Antonio López-Escámez Assoc. Prof. Dr. Patricia Perez Carpena

46. Table S36: Author Contributions

Author name	Contribution	Author name	Contribution
Stefan Schoisswohl, Ph.D.	Conceptualisation; investigation; formal analysis; methodology; project administration; supervision; visualisation; writing – original draft	Juan Martin-Lagos, M.D.	Investigation; writing – review & editing
Laura Basso, Ph.D.	Data curation; formal analysis; methodology; visualisation; writing – original draft	Marta Martinez-Martinez, M.D., Ph.D.	Investigation; writing – review & editing
Jorge Simoes, Ph.D.	Data curation; formal analysis; methodology; writing – review & editing	Nicolas Muller-Locatelli, M.D.	Investigation; writing – review & editing
Milena Engelke, M.Sc.	Data curation; formal analysis; methodology; visualisation; writing – original draft	Patrick Neff, Ph.D.	Conceptualisation; Methodology; writing – review & editing
Berthold Langguth, M.D.	Conceptualisation; funding acquisition; methodology; supervision; writing – review & editing	Uli Niemann, Dr. Ing.	Data curation; formal analysis; methodology; writing – review & editing
Birgit Mazurek, M.D., Ph.D	Conceptualisation; funding acquisition; methodology; writing – review & editing	Patricia Perez-Carpena, M.D., Ph.D.	Investigation; writing – review & editing
Jose Antonio Lopez-Escamez, M.D., Ph.D.	Conceptualisation; funding acquisition; methodology; writing – review & editing	Rüdiger Pryss, Ph.D.	Funding acquisition; investigation; methodology; software; writing – review & editing
Dimitrios Kikidis, M.D., Ph.D.	Conceptualisation; funding acquisition; methodology; writing – review & editing	Clara Puga, M.Sc.	Data curation; formal analysis; methodology; writing – review & editing
Rilana Cima, Ph.D.	Conceptualisation; funding acquisition; methodology; writing – review & editing	Paula Robles-Bolivar, M.Sc.	Investigation; writing – review & editing
Alberto Bernal-Robledano, M.Sc.	Investigation; writing – review & editing	Matthias Rose, Ph.D.	Investigation; writing – review & editing
Benjamin Boecking, Ph.D., DClinPsy.	Conceptualisation; methodology; investigation; writing – review & editing	Martin Schecklmann, Ph.D.	Conceptualisation; investigation; methodology; writing – review & editing
Jan Bulla, Ph.D.	Formal analysis; writing – review & editing	Tabea Schiele, M.Sc.	Investigation; writing – review & editing
Christopher R. Cederroth, Ph.D.	Funding acquisition; resources; writing – review & editing	Miro Schleicher, M.Sc.	Data curation; formal analysis; methodology; writing – review & editing
Holger Crump, Dipl.-Soz.-Wiss	Conceptualisation; writing – review & editing	Johannes Schobel, Ph.D.	Investigation; software; writing – review & editing
Sam Denys, Ph.D.	Investigation; writing – review & editing	Myra Spiliopoulou, Dr. habil.	Funding acquisition; data curation, formal analysis; writing – review & editing
Alba Escalera-Balsera, M.Sc.	Investigation; writing – review & editing	Sabine Stark, Dipl.-Psych.	Investigation; writing – review & editing
Alvaro Gallego-Martinez, Ph.D.	Investigation; writing – review & editing	Susanne Staudinger, M.A.	Conceptualisation; project administration; investigation; writing – review & editing
Silvano Gallus, Ph.D.	Funding acquisition; writing – review & editing	Alexandra Stege, Ph.D.	Investigation; writing – review & editing
Hazel Goedhart, M.Sc	Conceptualisation; writing – review & editing	Beat Toedtli, Ph.D.	Formal analysis; validation; writing – review & editing
Leyre Hidalgo-Lopez, M.D.	Investigation; writing – review & editing	Ilias Trochidis, M.Sc.	writing – review & editing
Carlotta M. Jarach, M.Sc.	Data curation; formal analysis; methodology; writing – review & editing	Vishnu Unnikrishnan, M.Sc.	Data curation; formal analysis; methodology; writing – review & editing
Hafez Kader, M.Sc.	Data curation; formal analysis; methodology; writing – review & editing	Evgenia Vassou, M.Sc.	Investigation; writing – review & editing

Michael Koller, Ph.D.	Conceptualisation; writing – review & editing	Nicolas Verhaert, M.D, Ph.D.	Investigation; writing – review & editing
Alessandra Lugo, Ph.D.	Writing – review & editing	Carsten Vogel, M.Sc.	Investigation; methodology; software; writing – review & editing
Steven C. Marcrum, Ph.D.	Conceptualisation; investigation; writing – review & editing	Zoi Zachou, M.D.	Investigation; writing – review & editing
Nikos Markatos, B.Sc. (Honors)	Investigation; writing – review & editing	Winfried Schlee. Ph.D.	Conceptualisation; funding acquisition; formal analysis; methodology; project administration; supervision; visualisation; writing – original draft

Note. All authors fulfilled the necessary requirement for authorship and agreed to be fully accountable for all aspects of the present work. All authors read and approved the final manuscript.

47. Table S37: Criteria for HA indication

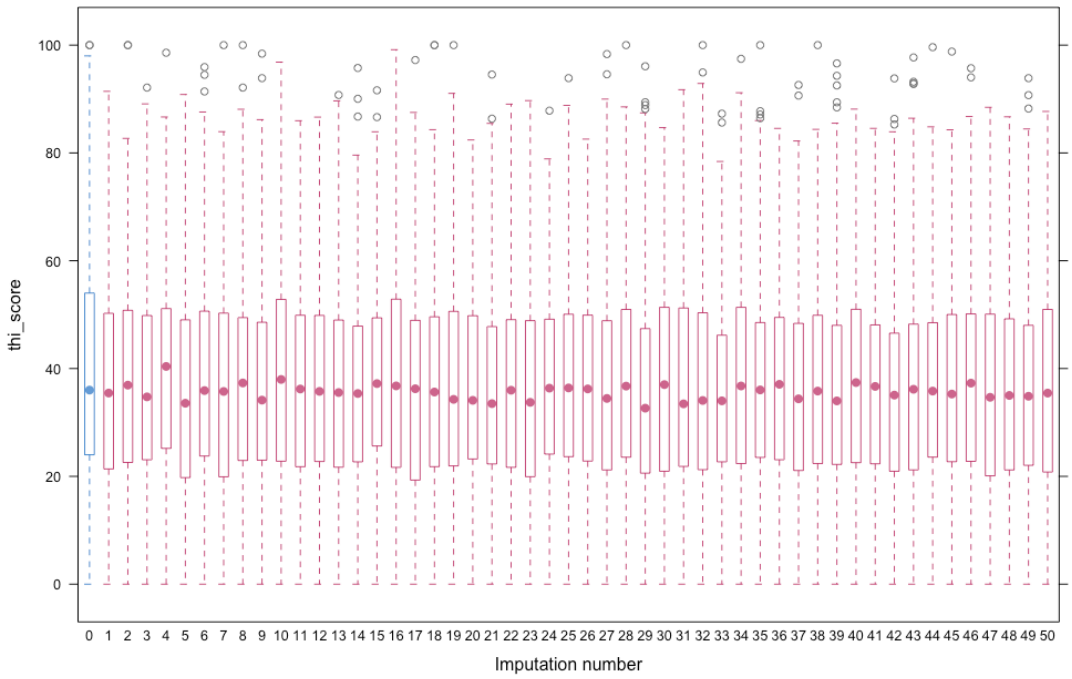
Frequency (Hz)	Minimum threshold (dB HL)	Maximum threshold (dB HL)
125	10	60
250	10	60
500	20	65
1000	25	70
2000	35	75
3000	40	80
4000	45	80
6000	45	80

Note. Minimum and maximum threshold (dB HL) per frequency used for the definition of HA indication. HA=Hearing aid.

48. *Table S38: Responsible Persons for the Conception of Treatments*

	Profession
Cognitive Behavioural Therapy	
Boecking, B.	Psychologist, Psychotherapist
Cima, R.	Psychologist, Psychotherapist
Schecklmann, M.	Psychologist, Psychotherapist
Hearing Aid	
Dettling-Papargyris, J.	Hearing aid acoustician
Kikidis, D.	Audiologist
Marcrum, S. C.	Audiologist
Mazurek, B.	ENT-Physician
Oppel, K.	Hearing aid acoustician
Schiele, T.	Doctoral student
Schlee, W.	Psychologist
Structured Counselling	
Engelke, M.	Psychologist
Schlee, W.	Psychologist
Sound Therapy	
Neff, P.	Psychologist
Schlee, W.	Psychologist

49. *Figure S11: Box-and-whisker Plot of Observed and Imputed THI Values*



Note. Blue (0): Distribution of observed THI values (all visits). Red (1-50): Distribution of imputed THI values in all imputed data sets (all visits). THI = Tinnitus Handicap Inventory.

50. References

Probst T, Pryss RC, Langguth B, Spiliopoulou M, Landgrebe M, Vesala M, Harrison S, Schobel J, Reichert M, Stach M and Schlee W. Outpatient tinnitus clinic, self-help web platform, or mobile application to recruit tinnitus study samples? *Frontiers in Aging Neuroscience* 2017; *9*: 113.

51. Published Study Protocol & Statistical Analysis Plan

Study Protocol

Schoisswohl S, Langguth B, Schecklmann M, *et al.* Unification of Treatments and Interventions for Tinnitus Patients (UNITI): a study protocol for a multi-center randomized clinical trial. *Trials* 2021; 22: 875.

https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-021-05835-z

Statistical Analysis Plan

Simoes JP, Schoisswohl S, Schlee W, *et al.* The statistical analysis plan for the unification of treatments and interventions for tinnitus patients randomized clinical trial (UNITI-RCT). *Trials* 2023; 24: 472

https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-023-07303-2

52. Ethics approvals

Universität Regensburg

Ethikkommission
bei der Universität Regensburg

Ethikkommission · Universität Regensburg · 93040 Regensburg

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17.05.2021

Unser Zeichen: 20-1936_2-101

Beratung nach § 15 Abs. 1 Berufsordnung für die Ärzte Bayerns – Nachträgliche Änderung vom *10.05.2021*

für das

Forschungsvorhaben	**UNification of treatments and Interventions for TInnitus patients – Randomized Clinical Trial (UNITI-RCT)**
Antragssteller	Stefan Schoisswohl, BSc MSc

Die Ethikkommission nimmt die nachträglichen Änderungen am o.g. Forschungsvorhaben zur Kenntnis. Eine erneute inhaltliche Bewertung ist nach geltendem Recht nicht vorgesehen.

Diese Entscheidung erging durch den Vorsitzenden der Ethikkommission im Benehmen mit der Geschäftsstelle im beschleunigten Verfahren.

Es wird auf folgendes grundsätzlich hingewiesen:

Die ärztliche und juristische Verantwortung verbleibt beim Forscher und seinen Mitarbeitern.

Die Auflagen der Deklaration von Helsinki des Weltärztebundes in ihrer aktuellen Fassung hinsichtlich ethischen und rechtlichen Aspekten biomedizinischer Forschung am Menschen sind strikt zu beachten.

Die Ethikkommission erwartet bei Interventionsstudien, dass ihr alle schwerwiegenden oder unerwarteten unerwünschten Ereignisse (u.a. Todesfälle), die während der Studie auftreten und die Sicherheit der Studienteilnehmer oder die Durchführung der Studie beeinträchtigen können, unverzüglich schriftlich mitgeteilt werden. Dieses sollte in Verbindung mit einer Stellungnahme des Antragsstellers geschehen, ob aus seiner Sicht die Nutzen-Risiko-Relation des Vorhabens verändert ist.

Die Ethikkommission bittet darum, dass ihr der Abbruch oder Abschluss einer Studie mitgeteilt werden.

Dieses Schreiben ist mit den Studienunterlagen jederzeit sorgfältig aufzubewahren. Duplikate oder Abschriften dieses Schreibens können im Nachhinein nicht erstellt werden.

Auf die Rechtspflichten zum Umgang mit dienstlichem Schriftgut bzw. Urkunden wird verwiesen.

Die Ethikkommission bestätigt die Bearbeitung gemäß der GCP/ICH-Richtlinien.

Die Ethikkommission empfiehlt im Einklang mit der Deklaration von Helsinki nachdrücklich die Registrierung der Studie vor Studienbeginn in einem öffentlich zugänglichen Register, das die von der WHO geforderten Voraussetzungen erfüllt.

Falls kein gesetzlicher Kostenbefreiungstatbestand greift, wird ein gesonderter Kostenbescheid für die Gebühren und Auslagen der Ethikkommission ergehen.

Die Übermittlung personenbezogener Daten einschließlich DNA-tragender Biomaterialien in datenschutzrechtlich unsichere Drittstaaten, wie etwa die USA, bedarf einer gesonderten datenschutzrechtlichen Beurteilung und Risikoaufklärung.

Datenschutzrecht wird durch die Ethikkommission grundsätzlich nur kursorisch geprüft. Dieses Votum ersetzt mithin nicht die Konsultation des zuständigen Datenschutzbeauftragten.

Mit dem Urteil des Europäischen Gerichtshofs vom 16. Juli 2020 [Aktenzeichen C3-11/18] stellen die Regelungen des EU-US-Privacy Shield insbesondere vor dem Hintergrund des Clarifying Lawful Overseas Use of Data Act (CLOUD Act) bzw. des Foreign Surveillance Act (FISA) keinen tauglichen Rechtsrahmen mehr dar. Es sollte seitens der Verantwortlichen im Einzelfall geprüft werden, inwieweit personenbezogene/personenbeziehbare Daten (also auch i.S.d. Art. 4 Abs. 5 DSGVO pseudonymisierte Datensätze) rechtssicher entweder auf Basis geeigneter Garantien (etwa verbindlicher Unternehmensregeln, Standardvertragsklauseln oder auf Basis einer ausdrücklichen Einwilligung nach erfolgter Risiko-Aufklärung nach Art. 49 Abs. 1 lit. a) DSGVO) übermittelt werden können. Es bleiben v.a. hinsichtlich der Standardvertragsklauseln die Auswirkungen des Urteils und die voraussichtlich folgenden regulatorischen Leitlinien seitens der zuständigen Behörden aufmerksam zu verfolgen. Es ist daher den Sponsoren dringend zu raten, sich mit dem zuständigen Landesbeauftragten für den Datenschutz abzustimmen.

Mit freundlichen kollegialen Grüßen

Prof. Edward K. Geissler, PhD
Vorsitzender

Anlage

ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
1η Υ.ΠΕ ΑΤΤΙΚΗΣ
ΓΕΝ.ΝΟΣ/ΜΕΙΟ ΑΘΗΝΑΣ
«ΙΠΠΟΚΡΑΤΕΙΟ»

Ε.Σ. 47ο/26-1-2021

ΕΠΙΣΤΗΜΟΝΙΚΟ ΣΥΜΒΟΥΛΙΟ

ΠΡΑΚΤΙΚΟ 47ο/26-1-2021

Της Συνεδρίασης του Επιστημονικού Συμβουλίου του Γ.Ν.Α. «ΙΠΠΟΚΡΑΤΕΙΟ» στις 26/1/2021, ημέρα Τρίτη και ώρα έναρξης 13.30.

Με την υπ' αριθμ. 1034/22-1-2021 πρόσκληση του Προέδρου του Επιστημονικού Συμβουλίου κ. Δημητρίου Πετρά, κλήθηκαν και παρέστησαν στη Συνεδρίαση οι κ.κ.

1. Πετράς Δημήτριος
   Δ/ντής Νεφρολογικού Τμήματος
2. Πηρουνάκη Μαρία
   Δ/ντρια Παθολογίας
3. Μαρκογιαννάκης Χαρίδημος
   Επιμ. Β΄ Χειρουργικής
4. Γαλιατσάτος Νικόλαος
   Βιοχημικός πρ. Προϊστάμενος Βιοχημικού Τμ.
5. Κάπελλα Μαρία
   Δ/ντρια Νοσηλευτικής Υπηρεσίας
6. Παύλου Ευθυμία
   Τεχνολόγος ΤΕ Προϊσταμένη Ιατρικών Εργ/ρίων

Οι κ.κ. Βολτέας Σπυρίδων, Χρυσοβέργης Αριστείδης και Καραθανάσης Παναγιώτης απουσίασαν, λόγω κωλύματος.

Επίσης παρέστη η κα Ζέλκα Ευθυμία, ως Γραμματέας.

Μετά τη διαπίστωση της νόμιμης απαρτίας ο Πρόεδρος του Επιστημονικού Συμβουλίου, κηρύσσει την έναρξη της 47ης Συνεδρίασης με τα παρακάτω θέματα:

ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
1η Υ.ΠΕ ΑΤΤΙΚΗΣ
ΓΕΝ.ΝΟΣ/ΜΕΙΟ ΑΘΗΝΑΣ
«ΙΠΠΟΚΡΑΤΕΙΟ»

Ε.Σ. 47ο/26-1-2021

ΕΠΙΣΤΗΜΟΝΙΚΟ ΣΥΜΒΟΥΛΙΟ

Ε.Η.Δ. 12ο Έγκριση διεξαγωγής Κλινικής Έρευνας με κωδικό UNITI-RCTκαι τίτλο: ΄΄Ενοποίηση θεραπειών και παρεμβάσεων για ασθενείς με εμβοές (UNITI)-τυχαιοποιημένη κλινική δοκιμή (RCT)΄΄, με Επιστημονικά Υπεύθυνο τον Αν. Καθηγητή Ω.Ρ.Λ. κ. Αθανάσιο Μπίμπα.

Μετά από τη θετική εισήγηση της Επιτροπής Έρευνας κ΄ Πρωτοκόλλων, υπό την Προεδρία του Καθηγητή κ. Ιωάννη Κοσκίνα

Ομόφωνα εγκρίνει

Τη διεξαγωγή της Κλινικής Έρευνας με κωδικό UNITI-RCTκαι τίτλο: ΄΄Ενοποίηση θεραπειών και παρεμβάσεων για ασθενείς με εμβοές (UNITI)-τυχαιοποιημένη κλινική δοκιμή (RCT)΄΄, με Επιστημονικά Υπεύθυνο τον Αν. Καθηγητή Ω.Ρ.Λ. κ. Αθανάσιο Μπίμπα.

Ο ΠΡΟΕΔΡΟΣ
ΕΠΙΣΤΗΜΟΝΙΚΟΥ ΣΥΜΒΟΥΛΙΟΥ

ΔΗΜΗΤΡΙΟΣ ΠΕΤΡΑΣ

ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
1η Υ.ΠΕ ΑΤΤΙΚΗΣ
ΓΕΝ.ΝΟΣ/ΜΕΙΟ ΑΘΗΝΑΣ
«ΙΠΠΟΚΡΑΤΕΙΟ»

Ε.Σ. 47ο/26-1-2021

ΕΠΙΣΤΗΜΟΝΙΚΟ ΣΥΜΒΟΥΛΙΟ

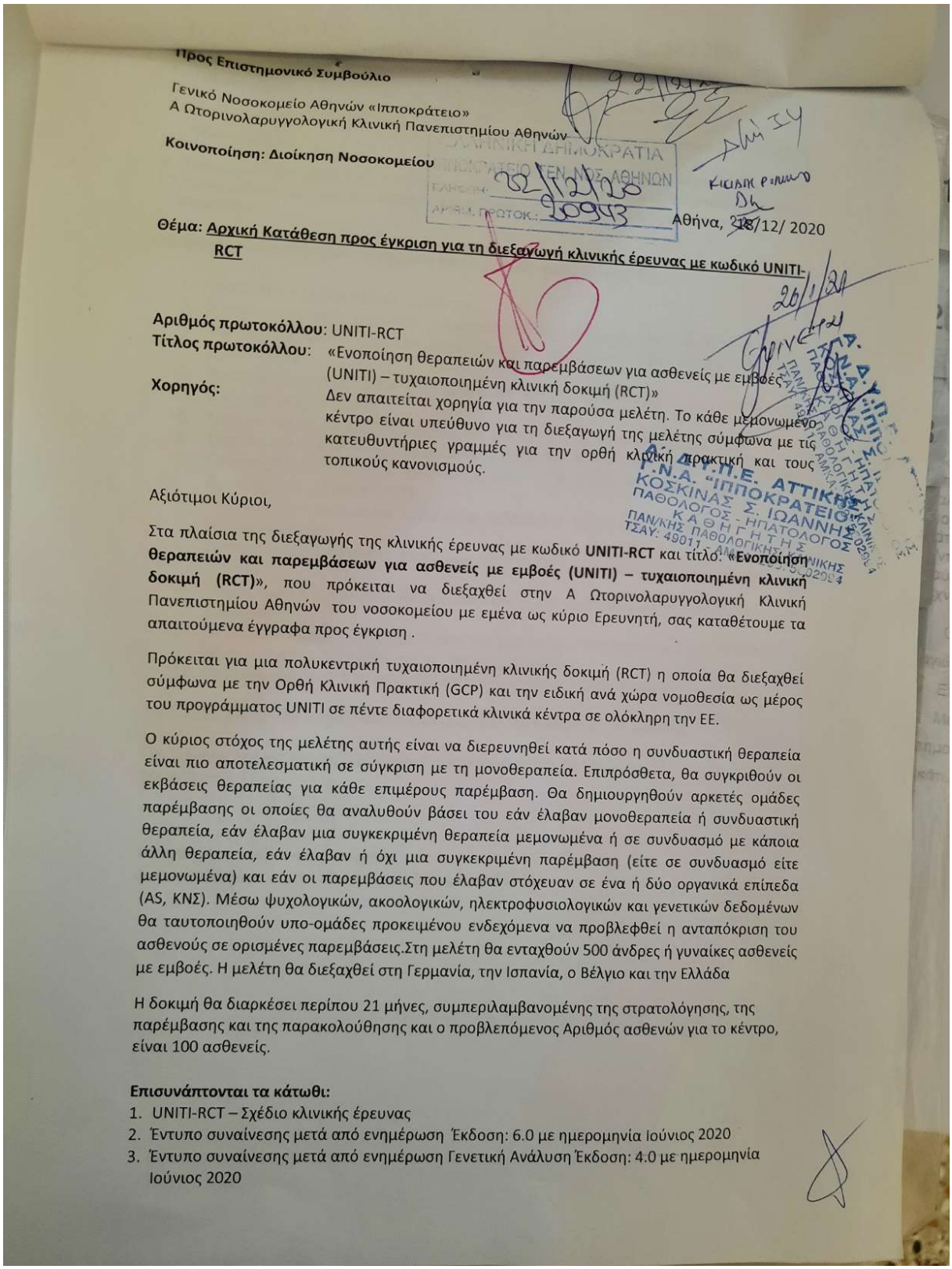
Μη υπάρχοντος άλλου θέματος προς συζήτηση, ο κ. Πρόεδρος του Επιστημονικού Συμβουλίου λύει τη Συνεδρίαση.

Η ΓΡΑΜΜΑΤΕΑΣ Ε.Σ.

ΖΕΛΚΑ ΕΥΘΥΜΙΑ

Ο ΠΡΟΕΔΡΟΣ ΤΟΥ Ε.Σ.

ΔΗΜΗΤΡΙΟΣ ΠΕΤΡΑΣ



Προς Επιστημονικό Συμβούλιο

Γενικό Νοσοκομείο Αθηνών «Ιπποκράτειο»
Α Ωτορινολαρυγγολογική Κλινική Πανεπιστημίου Αθηνών

Κοινοποίηση: Διοίκηση Νοσοκομείου

ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
ΓΕΝ. ΝΟΣ. ΑΘΗΝΩΝ
ΑΡΙΘΜ. ΠΡΩΤΟΚ.: 22/12/20 20943

Αθήνα, 18/12/ 2020

Θέμα: Αρχική Κατάθεση προς έγκριση για τη διεξαγωγή κλινικής έρευνας με κωδικό UNITI-RCT

Αριθμός πρωτοκόλλου: UNITI-RCT
Τίτλος πρωτοκόλλου: «Ενοποίηση θεραπειών και παρεμβάσεων για ασθενείς με εμβοές (UNITI) – τυχαιοποιημένη κλινική δοκιμή (RCT)»

Χορηγός: Δεν απαιτείται χορηγία για την παρούσα μελέτη. Το κάθε μεμονωμένο κέντρο είναι υπεύθυνο για τη διεξαγωγή της μελέτης σύμφωνα με τις κατευθυντήριες γραμμές για την ορθή κλινική πρακτική και τους τοπικούς κανονισμούς.

Α.Π.Γ.Υ.Π.Ε. ΑΤΤΙΚΗΣ
Γ.Ν.Α. "ΙΠΠΟΚΡΑΤΕΙΟ"
ΚΟΣΚΙΝΑΣ Σ. ΙΩΑΝΝΗΣ
ΠΑΘΟΛΟΓΟΣ - ΗΠΑΤΟΛΟΓΟΣ
ΠΑΝ/ΚΗΣ ΠΑΘΟΛΟΓΙΚΗΣ ΑΜΟΛΟΓΙΚΗΣ
ΤΣΑΥ: 49011

Αξιότιμοι Κύριοι,

Στα πλαίσια της διεξαγωγής της κλινικής έρευνας με κωδικό **UNITI-RCT** και τίτλο: «**Ενοποίηση θεραπειών και παρεμβάσεων για ασθενείς με εμβοές (UNITI) – τυχαιοποιημένη κλινική δοκιμή (RCT)**», που πρόκειται να διεξαχθεί στην Α Ωτορινολαρυγγολογική Κλινική Πανεπιστημίου Αθηνών του νοσοκομείου με εμένα ως κύριο Ερευνητή, σας καταθέτουμε τα απαιτούμενα έγγραφα προς έγκριση .

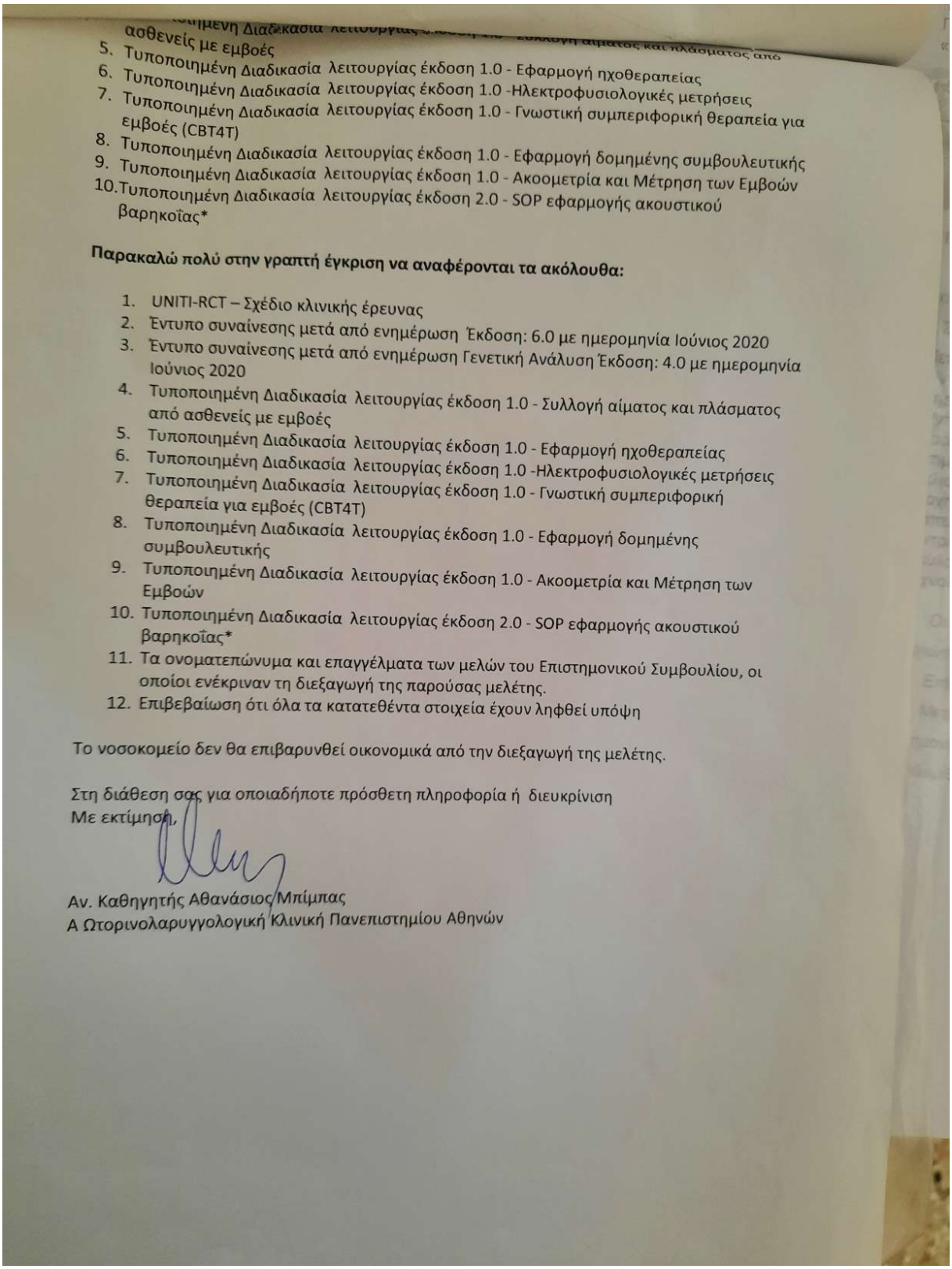
Πρόκειται για μια πολυκεντρική τυχαιοποιημένη κλινικής δοκιμή (RCT) η οποία θα διεξαχθεί σύμφωνα με την Ορθή Κλινική Πρακτική (GCP) και την ειδική ανά χώρα νομοθεσία ως μέρος του προγράμματος UNITI σε πέντε διαφορετικά κλινικά κέντρα σε ολόκληρη την ΕΕ.

Ο κύριος στόχος της μελέτης αυτής είναι να διερευνηθεί κατά πόσο η συνδυαστική θεραπεία είναι πιο αποτελεσματική σε σύγκριση με τη μονοθεραπεία. Επιπρόσθετα, θα συγκριθούν οι εκβάσεις θεραπείας για κάθε επιμέρους παρέμβαση. Θα δημιουργηθούν αρκετές ομάδες παρέμβασης οι οποίες θα αναλυθούν βάσει του εάν έλαβαν μονοθεραπεία ή συνδυαστική θεραπεία, εάν έλαβαν μια συγκεκριμένη θεραπεία μεμονωμένα ή σε συνδυασμό με κάποια άλλη θεραπεία, εάν έλαβαν ή όχι μια συγκεκριμένη παρέμβαση (είτε σε συνδυασμό είτε μεμονωμένα) και εάν οι παρεμβάσεις που έλαβαν στόχευαν σε ένα ή δύο οργανικά επίπεδα (AS, ΚΝΣ). Μέσω ψυχολογικών, ακοολογικών, ηλεκτροφυσιολογικών και γενετικών δεδομένων θα ταυτοποιηθούν υπο-ομάδες προκειμένου ενδεχόμενα να προβλεφθεί η ανταπόκριση του ασθενούς σε ορισμένες παρεμβάσεις.Στη μελέτη θα ενταχθούν 500 άνδρες ή γυναίκες ασθενείς με εμβοές. Η μελέτη θα διεξαχθεί στη Γερμανία, την Ισπανία, ο Βέλγιο και την Ελλάδα

Η δοκιμή θα διαρκέσει περίπου 21 μήνες, συμπεριλαμβανομένης της στρατολόγησης, της παρέμβασης και της παρακολούθησης και ο προβλεπόμενος Αριθμός ασθενών για το κέντρο, είναι 100 ασθενείς.

Επισυνάπτονται τα κάτωθι:

1. UNITI-RCT – Σχέδιο κλινικής έρευνας
2. Έντυπο συναίνεσης μετά από ενημέρωση Έκδοση: 6.0 με ημερομηνία Ιούνιος 2020
3. Έντυπο συναίνεσης μετά από ενημέρωση Γενετική Ανάλυση Έκδοση: 4.0 με ημερομηνία Ιούνιος 2020



ασθενείς με εμβοές
5. Τυποποιημένη Διαδικασία λειτουργίας έκδοση 1.0 - Εφαρμογή ηχοθεραπείας
6. Τυποποιημένη Διαδικασία λειτουργίας έκδοση 1.0 -Ηλεκτροφυσιολογικές μετρήσεις
7. Τυποποιημένη Διαδικασία λειτουργίας έκδοση 1.0 - Γνωστική συμπεριφορική θεραπεία για εμβοές (CBT4T)
8. Τυποποιημένη Διαδικασία λειτουργίας έκδοση 1.0 - Εφαρμογή δομημένης συμβουλευτικής
9. Τυποποιημένη Διαδικασία λειτουργίας έκδοση 1.0 - Ακοομετρία και Μέτρηση των Εμβοών
10. Τυποποιημένη Διαδικασία λειτουργίας έκδοση 2.0 - SOP εφαρμογής ακουστικού βαρηκοΐας*

Παρακαλώ πολύ στην γραπτή έγκριση να αναφέρονται τα ακόλουθα:

1. UNITI-RCT – Σχέδιο κλινικής έρευνας
2. Έντυπο συναίνεσης μετά από ενημέρωση Έκδοση: 6.0 με ημερομηνία Ιούνιος 2020
3. Έντυπο συναίνεσης μετά από ενημέρωση Γενετική Ανάλυση Έκδοση: 4.0 με ημερομηνία Ιούνιος 2020
4. Τυποποιημένη Διαδικασία λειτουργίας έκδοση 1.0 - Συλλογή αίματος και πλάσματος από ασθενείς με εμβοές
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11. Τα ονοματεπώνυμα και επαγγέλματα των μελών του Επιστημονικού Συμβουλίου, οι οποίοι ενέκριναν τη διεξαγωγή της παρούσας μελέτης.
12. Επιβεβαίωση ότι όλα τα κατατεθέντα στοιχεία έχουν ληφθεί υπόψη

Το νοσοκομείο δεν θα επιβαρυνθεί οικονομικά από την διεξαγωγή της μελέτης.

Στη διάθεση σας για οποιαδήποτε πρόσθετη πληροφορία ή διευκρίνιση
Με εκτίμηση,

Αν. Καθηγητής Αθανάσιος Μπίμπας
Α Ωτορινολαρυγγολογική Κλινική Πανεπιστημίου Αθηνών

4. Τυποποιημένη Διαδικασία λειτουργίας έκδοση 1.0 - Συλλογή αίματος και πλάσματος από ασθενείς με εμβοές
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Το νοσοκομείο δεν θα επιβαρυνθεί οικονομικά από την διεξαγωγή της μελέτης.

Στη διάθεση σας για οποιαδήποτε πρόσθετη πληροφορία ή διευκρίνιση
Με εκτίμηση,

Αν. Καθηγητής Αθανάσιος Μπίμπας
Α Ωτορινολαρυγγολογική Κλινική Πανεπιστημίου Αθηνών

DICTAMEN ÚNICO EN LA COMUNIDAD AUTÓNOMA DE ANDALUCÍA

D/Dª: ANTONIO SALMERON GARCIA como secretario/a del CEIM/CEI Provincial de Granada

CERTIFICA

Que este Comité ha evaluado la propuesta del promotor/investigador (No hay promotor/a asociado/a) para realizar el estudio de investigación titulado:

TÍTULO DEL ESTUDIO:	Unificación de tratamientos e intervenciones para pacientes con tinnitus - UNification of treatments and Interventions for TInnitus patients ,(UNITI)
Protocolo, Versión:	1
HIP, Versión:	1
CI, Versión:	1

Y que considera que:

Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio y se ajusta a los principios éticos aplicables a este tipo de estudios.

La capacidad del/de la investigador/a y los medios disponibles son apropiados para llevar a cabo el estudio.

Están justificados los riesgos y molestias previsibles para los participantes.

Que los aspectos económicos involucrados en el proyecto, no interfieren con respecto a los postulados éticos.

Y que este Comité considera, que dicho estudio puede ser realizado en los Centros de la Comunidad Autónoma de Andalucía que se relacionan, para lo cual corresponde a la Dirección del Centro correspondiente determinar si la capacidad y los medios disponibles son apropiados para llevar a cabo el estudio.

Lo que firmo en Granada a 28/01/2021

D/Dª. ANTONIO SALMERON GARCIA, como Secretario/a del CEIM/CEI Provincial de Granada

Código Seguro De Verificación:	919efafa5c41c421c6bd4888cff8f4a36303e263	Fecha	28/01/2021
Normativa	Este documento incorpora firma electrónica reconocida de acuerdo a la Ley 59/2003, de 19 de diciembre, de firma electrónica.		
Firmado Por	Antonio Salmeron Garcia		
Url De Verificación	https://www.juntadeandalucia.es/salud/portaldeetica/xhtml/ayuda/verificarFirmaDocumento.iface/code/919efafa5c41c421c6bd4888cff8f4a36303e263	Página	1/3

CERTIFICA

Que este Comité ha ponderado y evaluado en sesión celebrada el 26/01/2021 y recogida en acta 1/21 la propuesta del/de la Promotor/a (No hay promotor/a asociado/a), para realizar el estudio de investigación titulado:

TÍTULO DEL ESTUDIO:	Unificación de tratamientos e intervenciones para pacientes con tinnitus - UNification of treatments and Interventions for TInnitus patients ,(UNITI)
Protocolo, Versión:	1
HIP, Versión:	1
CI, Versión:	1

Que a dicha sesión asistieron los siguientes integrantes del Comité:

Presidente/a

D/Dª. AURORA BUENO CAVANILLAS

Vicepresidente/a

D/Dª. Paloma Muñoz de Rueda

Secretario/a

D/Dª. ANTONIO SALMERON GARCIA

Vocales

D/Dª. PATRICIA GALVEZ MARTIN
D/Dª. Juan Ramón Delgado Pérez
D/Dª. Berta Gorlat Sánchez
D/Dª. José Dario Sánchez López
D/Dª. Sonia Dominguez Almendros
D/Dª. Juan Mozas Moreno
D/Dª. SALVADOR ARIAS SANTIAGO
D/Dª. MARIA ESPERANZA DEL POZO GAVILAN
D/Dª. Francisco OValle Ravassa
D/Dª. Esther Espínola García
D/Dª. ANTONIO MORALES ROMERO
D/Dª. MARTA CUADROS CELORRIO
D/Dª. MARIA ANGELES GARCIA LIROLA
D/Dª. Encarnación Martínez García
D/Dª. FRANCISCO LUIS MANZANO MANZANO
D/Dª. MIGUEL LÓPEZ GUADALUPE
D/Dª. JUAN ROMERO COTELO
D/Dª. MANUEL MARTIN DIAZ
D/Dª. ANGEL COBOS VARGAS
D/Dª. LUIS MIGUEL DOMENECH GIL
D/Dª. MARIA DEL ROCIO MORON ROMERO
D/Dª. Luis Javier Martínez González
D/Dª. JESÚS CARDONA CONTRERAS
D/Dª. Pilar Guijosa Campos
D/Dª. Miguel Álvarez López
D/Dª. RAFAEL MARIN JIMENEZ
D/Dª. JOAQUINA MARTINEZ GALAN
D/Dª. MARÍA DOLORES GARCÍA VALVERDE
D/Dª. ESTHER MOLINA RIVAS
D/Dª. ANTONIO JUAN PÉREZ FERNÁNDEZ
D/Dª. JUAN CARLOS NAVARRO BARRIOS

Código Seguro De Verificación:	919efafa5c41c421c6bd4888cff8f4a36303e263	Fecha	28/01/2021
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D/Dª. ANTONIO JIMENEZ PACHECO

Que dicho Comité, está constituido y actua de acuerdo con la normativa vigente y las directrices de la Conferencia Internacional de Buena Práctica Clínica.

Lo que firmo en Granada a 28/01/2021

Código Seguro De Verificación:	919efafa5c41c421c6bd4888cff8f4a36303e263	**Fecha**	28/01/2021
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Leuven, 15 Oct 2021

Ethics Committee
Research UZ/KU Leuven
Herestraat 49
B 3000 Leuven (Belgium)
Tel +32 16 34 86 00
Email : ec@uzleuven.be

dr. Rilana Cima

Our reference:	EudraCT-nr:	Belg. Regnr:
S65058		B3222021000553

UNification of treatments and Interventions for TInnitus patients – Randomized Clinical Trial

Positive advice in accordance with the law of 7 May 2004 on experiments on the human person

Dear colleague

The Ethics Committee Research (EC Research) of University Hospitals Leuven (UZ Leuven) has examined and discussed the above mentioned dossier at its meeting of 12 Jul 2021.

After having consulted the additional information and/or adapted documents relating to this dossier, EC Research considers that the proposed study, as described in the protocol, is scientifically relevant and ethically justified. It therefore gives on 15 Oct 2021 a favourable opinion of this study.

EC Research emphasizes the responsibility of the PI/promotor of this study concerning the privacy of the person/patient data in contacts with patients, or when viewing patient data, including the correct implementation thereof by coworkers and students. The PI/promotor is responsible for the implementation of the project proposal in accordance with applicable laws and regulations including, but not limited to, the EU regulation 2016/679 (General Data Protection Regulation), the Belgian Law on patients' rights of 22/8/2002, and the policy of the institution where the research will be carried out.

EC Research refers to the ICH/GCP guidelines on its website, and confirms that a GCP-training is required from each investigator. It is the responsibility of the principal investigator that each member of the study team has a valid GCP-certificate.

For the assessment of this dossier, documents/answers submitted on 22 Jun 2021, 24

Sep 2021, 08 Oct 2021 and 13 Oct 2021 have been taken into account.

The favourable advice concerns:

Protocol:
version 2.3 dd 13Oct2021
Informed Consent Form:
ICF v2.2 dd 01Oct2021 Nl + Fr + En
Other subject information documentation:
ATAQ version received dd 22Jun2021 Nl
BFI2-NL version received dd 22Jun2021 Nl
CGI version received dd 22Jun2021 Nl
ESIT-SQ version 1 dd Oct2018 Nl
FTQ version received dd 22Jun2021Nl
GÜF version received dd 22Jun2021 Nl
Mini-SOISES version received dd 22Jun2021 Nl
Mini-TQ version dd 02Feb2017
PHQ-9 version received dd 22Jun2021 Nl
TFI v4 post validation Nl
Tinnitus Handicap Inventaris version received dd 22Jun2021 Nl
Tinnitusernst version received dd 22Jun2021 Nl
TSCHQ : version received dd 22Jun2021 Nl
WHOQOL-BREF : version received dd 22Jun2021 Nl
Tinnitus daily diary version received dd 24Sep2021 Nl
Investigator's brochure/scientific leaflet:
SOP Electrophysiological Measurements v1.0
SOP Audiometry and Tinnitometry v1.0
SOP Blood and plasma collection from tinnitus patients v1.0
SOP Cognitive Behavioral Therapy for Tinnitus (CBT4T) v1.0
SOP Hearing Aid Fitting SOP* v2.0
SOP Sound Therapy App v1.0
SOP Structured Counselling App v1.0
Proof of "no-fault" insurance cover:
dd 01Jan2020 - 31Dec2022
Recruitment material:
recruitment flyer version 1.1 dd 23Sep2021 Nl
GDPR questionnaire:
dd 07Oct2021

EC Research confirms working in accordance with the ICH-GCP principles (International Conference on Harmonization Guidelines on Good Clinical Practice), the latest version of the Declaration of Helsinki, the Oviedo Convention on Human Rights and Biomedicine and applicable laws and regulations.

EC Research confirms that - in case of conflict of interest - involved members do not take part in the vote concerning the study.

List of members: see appendix.

Points of concern: (if applicable)

The conformity of translated documents compared to the Dutch documents, is the responsibility of the sponsor.

We would like to draw your attention to the fact that EC Research expects her initial comments to be taken into account ab initio at the next submission by the same sponsor.

*Provided that there is a **Clinical Trial Agreement**, the study can only start when the Clinical Trial Agreement has been approved and signed by the CEO of UZ Leuven (and/or by an authorized representative of KU Leuven R&D).*

Studies with investigational medicinal products and certain studies with "medical devices" should be submitted by the client (PI or sponsor) to the FAMHP (Federal Agency for Medicines and Health Products).

Studies with investigational medicinal products are only allowed to be conducted, provided that the minister (FAMHP) does not state objections within legal deadlines as described in art. 13 of the Belgian law of 7/5/2004 concerning experiments on human people.

Certain studies using medical devices are also covered by legal deadlines (KB of 17/3/2009). Please consult the FAMHP website for more information: www.fagg-afmps.be.

Research on embryos in vitro is covered by the law of May 11, 2003. Before the research project can start, such research also requires a positive advice of the Federal Committee for medical and scientific research on embryos in vitro.

Please take into account the regulations of the hospital concerning tissue management and the regulations of the law of December 19, 2008.
This favourable advice of EC Research does not imply that it will assume responsibility for the planned study. You will remain responsible for the study. In addition, you should ensure that your opinion as an involved researcher is reproduced in publications, reports for the government, etc. which are the result of this study. You are reminded that concerning clinical studies, any observed serious event needs to be reported immediately to the sponsor and the ethics committee, even if the causal relationship with the study is unclear.

The EC approval given for a specific project, is valid for one year. We request you to inform us if the study will not be initiated or if the study does not start within 1 year after approval.

*If the study will not be terminated within a year, the ICH-GCP demands that an **annual progress report** will be provided to EC Research.*

*Finally, we request you to report the termination (early or planned) of the study within the legal deadlines and provide the **Clinical Study Report** (CSR) to EC Research.*

In case of a clinical trial (EudraCT), please be informed that the results must be published in the European Clinical Trial Register. The report of these results can be sent to the EC Research as the CSR.

Yours sincerely,

Prof. Dr. Minne Casteels
Chair
Ethics Committee Research UZ Leuven

Cc:
FAMHP (Federal Agency for Medicines and Health Products)

CTC (Clinical Trial Center UZ Leuven)

List of members EC Research UZ/KU Leuven

Chair	prof. dr. Maria-Reinhilde Casteels	Clinical Pharmacology
Vice chair	prof. dr. Dominique Bullens	Paediatrics
	De heer Aernout De Raemaeker	Medical Legislation alternate
	De heer Jean-Jacques Derèze	Medical Legislation alternate
	De heer Mathijs Swaak	Healthy volunteer repres.
	Mevr. Angélique Rézer	Medical Legislation alternate
	Mevr. Annick Vanclooster	Nurse
	Mevr. Katelijne Van Overwalle	Pt representative (alternate)
	Mevr. Lia De Wilde	Pt representative (alternate)
	Mevr. Liliane Vandergeeten	Pt representative (alternate)
	Mevr. Marilien Vandeputte	Nurse
	Mevr. Michèle Dekervel	Medical Legislation alternate
	Mevr. Teresia De Fraye	Pt representative
	Mevr. Veerle Vanparys	Pharmacist (alternate)
	apr. Josse R. Thomas	Clinical Pharmacology
	dr. Kristel Van Landuyt	Reumatology
	dr. Lut De Groote	General Practitioner
	dr. Marleen Renard	Paediatrics
	prof. André Loeckx	Pt representative (alternate)
	prof. Ben Van Calster	Statistics
	prof. Guy Bosmans	Clinical Psycology (alternate)
	prof. Pascal Borry	Ethics
	prof. dr. Anne Smits	Paediatrics
	prof. dr. Anne Uyttebroeck	Paediatrics
	prof. dr. Ariel Alonso	Statistics (alternate)
	prof. dr. Benoit Nemery	Pneumology
	prof. dr. Gregor Verhoef	Haematology
	prof. dr. Jan Verhaegen	Laboratory Medicine
	prof. dr. Jan de Hoon	Clinical Pharmacology
	prof. dr. Karin Sipido	Experimental Cardiology
	prof. dr. Koen Luyckx	Clinical Psycology (alternate)
	prof. dr. Maria Schetz	Intensive care
	prof. dr. Simon Brumagne	Physiotherapy
	prof. dr. Xavier Bossuyt	Immunology
	prof. dr. apr. Erwin Dreesen	Pharmacist (alternate)