A Prospective, Open-Label Trial of MHNA-003, a Smartphone-Delivered Cognitive Behavioral Therapy (CBT) Treatment, in Adults with Symptoms of Tinnitus	
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Registration ID:	NCT05696158
Product:	MHNA-003-001
Sponsor:	Mahana Therapeutics, Inc.
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Background

Mahana™ Tinnitus (MHNA-003) is a Digital Therapeutic (DTx) in development at Mahana Therapeutics. MHNA-003 provides CBT adapted for tinnitus via smartphone application.

CBT is a skills-based, present-focused, time-limited psychological therapy that examines thoughts, feelings, and behaviors which have an adverse impact on an individual's life, the context in which these occur, and the relationship among these factors. Within CBT, data driven strategies are then employed to systematically target these factors. CBT programs strive to build adaptive coping skills and interrupt problematic behaviors that are perpetuating the targeted symptoms (e.g., inactivity, negative self-referential cognitions, ruminations that maintain the depressive cycle, etc.). Decades of rigorous scientific evidence demonstrate the effectiveness of CBT for treating mood and anxiety disorders, substance abuse, and insomnia, as well as improving QoL and disease management among patients with chronic medical illnesses[1,2].

The efficacy of internet-based CBT programs for tinnitus is well documented. In a recent meta-analysis conducted by Beukes et al.,[3] It was found that internet-based CBT programs demonstrated a moderate effect size in reducing tinnitus distress. This effect was observed in comparison to both active and inactive control conditions across nine Randomized Controlled Trials (RCT) involving 1,165 tinnitus patients.

Objectives

The purpose of this study is to assess the safety and clinical outcomes for MHNA-003 used together with routine care in adult patients aged 18 and older with tinnitus or ringing in the ears.

Product-specific feedback and usage data will be collected in order to inform further development of MHNA-003.

Given the pilot study's open-label, single arm design, study findings should be interpreted as signals to explore in future randomized-controlled trials rather than identifying definitive clinical significance.

Study Design

This is a prospective, open-label study of the mobile app MHNA-003.

Between 125 and 250 participants will be enrolled. All enrolled participants will receive MHNA-003 in addition to their routine care.

Safety and clinical outcomes assessments will be collected bi-weekly for a total of four data collection timepoints.

A study design schematic is provided in Figure 1 below.

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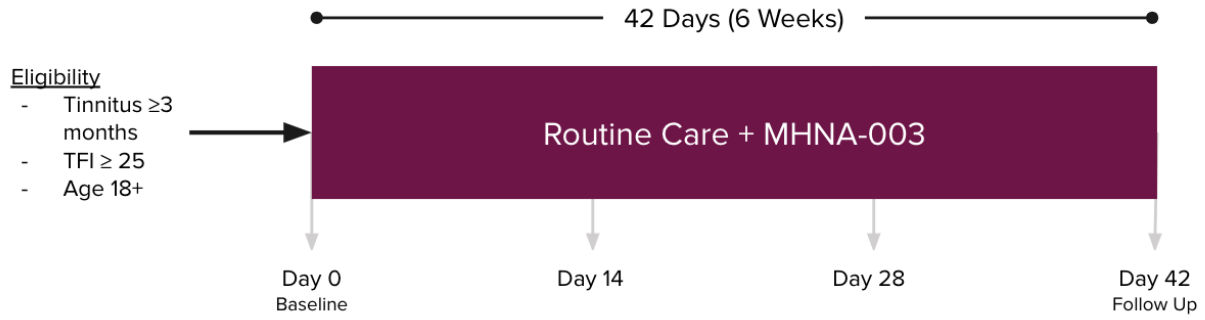
[1] Hofmann, S. G., Asnaani, A., Vonk, I. J., Sawyer, A. T., & Fang, A. (2012). The efficacy of cognitive behavioral therapy: A review of meta-analyses. Cognitive therapy and research, 36(5), 427-440

[2] Dobson, D., & Dobson, K. S. (2018). Evidence-based practice of cognitive-behavioral therapy. Guilford Publications.

[3] Beukes EW, Manchaiah V, Allen PM, Baguley DM, Andersson G. Internet-Based Interventions for Adults With Hearing Loss, Tinnitus, and Vestibular Disorders: A Systematic Review and Meta-Analysis. Trends Hear. 2019 Jan-Dec;23:2331216519851749.



All study activities are decentralized and will not require participants to visit a site in person. A centralized Principal Investigator and clinical study staff will conduct study activities remotely. Participants will complete all study activities remotely.

Measures

Primary outcomes are a change from baseline in Tinnitus Functional Index (TFI) and TFI responder rate at 6 weeks. A reduction of 13 points is considered clinically significant for the TFI.[4]

Eligibility

Participants must satisfy the following criteria before entering the study:

1. Participant scores ≥ 25 on the Tinnitus Functional Index.
2. Participant has experienced symptoms of tinnitus for at least 3 months.
3. Participant is at least 18 years of age at the time of consent.
4. Participant resides in the United States.
5. Participant is able to speak, read, and understand English.
6. Participant has access to an iOS or Android smartphone with the ability to complete study tasks.
7. Participant is able to commit the time required to complete therapy modules and study assessments.

Participants who meet any of the following criteria will be excluded from participating in the study:

1. Participant scores ≥2 on item 9 (suicidal thoughts) of the Beck's Depression Index (BDI).
2. Participant has been hospitalized for psychiatric reasons within 12 months of screening.
3. Participant is currently enrolled in or plans to enroll in another clinical study that could impact outcomes of this trial.
4. Other exclusions may apply if determined by the clinical study team that participation may be impacted.

Sample Size

This study will enroll 125-250 total participants.

[4] Meikle MB, et al. *Ear Hear*. 2012;33(2):153-76

Intervention

MHNA-003 is an investigational software as a medical device (SaMD) built for mobile usage.

MHNA-003 comprises five total sessions. Each session includes several lessons which provide components of cognitive behavioral therapy.

We recommend that participants complete one lesson of MHNA-003 per day. One lesson takes approximately 10-15 minutes. At the recommended pace the study sessions will take participants approximately 30 days to complete all lessons. This study protocol includes twelve additional days (42 total study days) to accommodate unanticipated interruptions to therapy progress.

MHNA-003 is available via a downloadable application for iOS and Android smartphones. Access to MHNA-003 and technical assistance will be provided to participants at no charge.

MHNA-003 is considered a non-significant risk (NSR) device. The risks associated with using MHNA-003 are akin to those associated with using a mobile app for 10-15 minutes per day.

Statistical Analysis

Analyses of feasibility and participant-reported clinical outcomes primarily rely on descriptive statistics. Inferential statistics are used to explore potential preliminary associations. All statistical analyses are performed using Stata 18.0 and focus on the intent-to-treat population.

Baseline demographics and participant characteristics are summarized using descriptive statistics. Specifically, means, standard deviations (SD), and ranges are assessed for continuous variables and assessment scores typically treated as continuous. Data are presented as mean ± SD. For categorical data, n's and percentages are calculated.

Statistical analysis techniques are employed to evaluate changes in patient-reported outcomes over time. Magnitude and statistical significance for change from baseline are tested using single factor mixed effects linear GLS regression modeling. This type of model is able to handle missing data due to attrition and can also be utilized for complete datasets. The need for random effects is tested in all cases using the Hausman comparison[5] and Breusch and Pagan Lagrangian multiplier test.[6] The Breusch-Pagan and Cook-Weisberg test for heteroscedasticity[7] is also utilized. Mean, standard error of the mean, and 95% confidence intervals are calculated for changes from baseline. Wald chi-square tests assess the significance of changes from baseline over time.

Six-week responder rates are evaluated utilizing multiple imputation modeling to account for missing data. Responder rates are imputed in the ITT population utilizing logistic models. Four baseline factors are included in the imputation model: age, sex, baseline GAD-7 score, and baseline PHQ-8 score. It is possible that these help to describe relevant populations for level of outcome. In addition, program adherence is included as a covariate because outcome level is

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[5] Hausman JA. *Econometrica.* 1978;46:1251-1271.

[6] Breusch TS & Pagan AR. *Econometrica.* 1979;47(5):1287-1294.

[7] Cook RD & Weisberg S. Biometrika. 1983;70(1):1-10.

hypothesized to be related to program adherence. Sensitivity analysis is performed by removing the auxiliary variables from the imputation regression. Standard error of the mean and 95% CI are calculated for the responder rates.