Study Protocol and Statistical Analysis Plan

Evaluation of Hearing Aid Benefit

Version 2.0

02/04/2022

NCT05198713

Evaluation of Hearing Aid Benefit

1 Background

In autumn 2020, Phonak released the first iteration of the Paradise line of hearing instruments with Audeo P. In the intervening time, Paradise has been extended to include Naida P, CROS P, and Audeo Life. Beginning in 2022, the Paradise line will be extended once again to include custom devices with Virto P. Performance of this feature set has been tested and validated in other form factors, and relevant claims have been substantiated during those studies, as well. Virto P has been determined to be technically and biologically equivalent to Audeo P; it is, therefore, not necessary to re-validate all functionality and re-substantiate all claims.

Despite the determination that Audeo P clinical data is generally applicable to Virto P, it is nevertheless advisable to collect clinical and usability data with Virto P to demonstrate that our devices provide a clinical benefit to the user relative to no device.

2 Objectives

Primary objective:

- To evaluate whether adults with moderate to severe hearing loss (N3/N4) can achieve speech understanding equivalent to their individual dB-opt at a typical conversational input level while using Virto P devices in quiet.

Secondary objectives:

- To evaluate whether Virto P hearing instruments provide improved speech intelligibility in noise compared to the unaided condition in a group of adults with moderate to severe hearing loss (i.e., N3/N4).

3 Description of the investigational device

The Virto P is a hearing aid on the Paradise platform and is worn in the ear canal. The microphone(s) pick(s) up sound waves, convert(s) them into an electrical signal which is sent to the Digital Signal Processor (DSP), which is part of the hybrid. The DSP applies the amplification to the electrical signal, which means that the amplitude of the signal gets modified. The modified electrical signal is forwarded to the external receiver, which is hold in the ear canal with the aid of an earpiece. The external receiver converts the electrical signal into an acoustic signal and submits it to the ear drum. An integrated Bluetooth antenna enables the hearing aid to also receive digital signals (e.g. streamed music), which will be processed in the same way.
The overall intended purpose of the device is to amplify and transmit sound ot the ear and thereby compensate for impaired hearing.

4 Design of the clinical investigation

This investigation is a single-center, single-group, open-label clinical investigation. The primary aim of the present investigation is to produce evidence of the clinical benefit of Virto P devices relative to the unaided condition. Because it is unethical to knowingly deprive a group of individuals with a sensory disability (hearing loss) from a well-established treatment (hearing instruments), this trial will rely on laboratory testing in the aided and unaided conditions rather than treatment and control groups to evaluate benefit.

5 Risks and benefits of the investigational device and clinical investigation

Virto P hearing instruments carry only minimal risks under normal use conditions and are intended to give the user auditory access to speech communication. There are no risks associated with the investigation procedures that are not associated with the use of the device. Participants in this investigation will benefit from the ability to hear and communicate in their daily lives, while experiencing only minimal risk associated with the use of the device.

6 Endpoints

Primary objective:

The NU-6 word lists are used extensively in the United States for clinical and research assessments of speech understanding and has been in use for over 50 years (Tillman, Carhart, Wilber, 1963). This test material was selected due to its long history of use in the United States as a measure of monosyllabic word recognition.

Performance on speech recognition tasks varies as a function of hearing loss (Guthrie and Mackersie, 2009). Not all patients will be able to reach 100% correct performance, regardless of the presentation level. Due to this variation, 'excellent' has been defined for this investigation as each individual participant's own maximum performance (PB-max). This investigation will aim to demonstrate equivalency on NU6 word recognition between aided performance at a typical level (65 dB(A)) and the participant's unaided PB-max.

Secondary objective:

The American English Matrix test was selected because it is an externally developed and validated speech test with a steep psychometric function. Because the test estimates an SNR-50, the steep psychometric function makes it a sensitive measure for comparing across multiple conditions. In this case, the test will be administered both with and without hearing aids. These results will be used to support the notion that hearing aids provide a clinical benefit (i.e., hearing speech in noise).

7 Inclusion and Exclusion Criteria

Subjects fulfilling all of the following inclusion criteria are eligible for the investigation:

- N3/N4 sensorineural hearing loss
- Willingness to travel to on-site appointments
- 18-100 years old
- Willingness to use custom hearing instruments
- Fluent in English

The presence of any one of the following exclusion criteria will lead to the exclusion of the subject:

- Cognitive impairment

8 Measurements and procedures

This investigation will evaluate the clinical benefit of the Virto P hearing instruments, and it will generate data to substantiate the claim that Virto P hearing instruments provide the end user with "excellent speech understanding." Virto P hearing instruments are custom, in-the-ear (ITE) devices produced by

Sonova AG under its flagship brand, Phonak. Virto P devices are intended to compensate for mild to profound hearing loss by amplifying speech and other acoustic input to a level that is audible, yet comfortable, for the patient.
One of the most important clinical benefits of any hearing instrument is to provide improved speech intelligibility in difficult listening situations. To evaluate this benefit, participants in this investigation will complete speech-in-noise testing in both an aided and unaided condition. If Virto P is providing the intended benefit, participants should, as a group, perform better in the aided condition than in the unaided condition.
For the purposes of generating data to substantiate the claim that Virto P provides "excellent speech understanding," 'excellent' has been defined as the best possible speech understanding score a user is able to achieve when asked to listen to and repeat words in quiet. This maximum level of understanding will be established for each participant in the unaided condition, and testing will be repeated at a conversational level in the aided condition. Equivalence (defined as +/- 10 %-age points) between these two measures will show that users can understand as much speech as their auditory system will permit when using Virto P and listening to speech at a typical intensity level.

9 Statistical design and analysis

The sample size for this investigation was determined based on the planned analysis for the primary objective. Sample size calculation was conducted in R using the TOSTER package. The code used to generate the sample size calculation is reproduced below.

```
TOSTER::powerTOSTpaired.raw(alpha = .05,
                            statistical_power = .8,
                            sdif = 12,
                            low_eqbound = -10,
                            high_eqbound = 10)
```

The calculation above assumes an equivalence margin of +/- 10 percentage points and a standard deviation of differences of 12. The power analysis described above yielded a sample size of 13 participants at a power of 0.8 and alpha of 0.05. An additional 3 participants will be recruited to account for potential attrition and/or missing data.

Speech intelligibility data for the primary and secondary objectives from all subjects will be analyzed. A separate analysis will be conducted for the speech intelligibility in quiet measure (primary objective) and the speech intelligibility in noise measure (secondary objective). Participants will not be grouped as a part of these analyses.

The principal investigator will conduct the analysis of the primary endpoint after data has been collected from all participants for all test conditions. This analysis will be conducted in the R statistical computing environment. The analysis will follow a two one-sample t-test procedure to test for equivalency between the aided NU6 performance in quiet and the unaided PB-max performance level. In this procedure, the two one-sample tests will compare the mean difference between the two test conditions to the equivalence margin of 10 percentage points. The two tests will differ only in their alternative hypothesis; one test have an alternative hypothesis that the mean difference is greater than the equivalence margin, the other that the mean difference is less. Rejection of both tests will be interpreted to indicate that the true mean difference is within the equivalence margin above/below zero.

The principal investigator will conduct the analysis of the secondary endpoint related to speech intelligibility in noise after all data has been collected from all participants in all test conditions. The analysis will be conducted in the R statistical computing environment. The analysis will use a paired t-test to compare the aided speech in noise performance to the unaided speech in noise performance.

10 Investigation Duration

The expected duration for each participant is ~2-3 weeks.

11 Data handling and management

This investigation will utilize electronic CRFs, including Microsoft Excel and Word files. For all CRFs, the participants will be identified only by an anonymous code, which will not include their real names, initials, birthdates, or other identifying information. The code list will be stored separately on a restricted access server maintained by Sonova USA. All investigators and study staff will have access to CRFs during the course of the investigation. Following the completion of this investigation, CRFs will be locked and maintained in the TMF.

Any paper-based data will be stored in a locked filing cabinet at the investigation site. All electronic data will be stored on an access-restricted server owned, operated, and maintained by Sonova USA. Servers used to store data in this investigation are physically located in the US.

The identifiable data kept at PARC will be destroyed as soon as the final analyses have been completed. The de-identified data will be kept for seven years after the publication of results. When the data are destroyed, paper records will be shredded by services provided at PARC. Electronic data will be encrypted as de-identified NOAH packages, where applicable, to be shared with Sonova Switzerland.

12 Amendments to the CIP

If it is necessary to make an amendment to this CIP, the changes to the CIP will be clearly identified with the date the change was made, and the version number will be incremented. Non-substantial amendments (e.g., correcting a typographical error) will be recorded as a minor version incrementation, whereas substantial amendments (e.g., a change to the study procedure or statistical plan) will be recorded as a major version incrementation. In an emergency situation, this CIP will be amended and updated only after participant health and safety have been assured and FDA/WIRB have been notified (as applicable).

13 Deviations from clinical investigation plan

Deviations from the CIP to protect the rights, safety and well-being of human participants under emergency circumstances may proceed without prior approval of the sponsor and the EC – such deviations will be documented and reported to the sponsor representative (Study Manager) and the EC as soon as possible. Apart from that the investigator is not allowed to deviate from this CIP unless that deviation does not influence the investigation data.

14 Device accountability

Copy from chapter 12.1(Accountability for investigational device)

The PI or authorized designee keep records documenting the following in a written process:

- Names of participants who received, used, returned, or disposed of device

- Date of receipt, identification, and quantity of each investigational device (batch/serial number or unique code)
- Expiry date (if applicable)
- Date(s) of use

The PI or authorized designee keep records documenting the following in a written process:

- Date on which the device was returned (if applicable)
- Date of return of unused, expired, or malfunctioning investigational devices (if applicable)
- Date and documentation of disposal of devices as per sponsor instructions (if applicable)

15 Informed consent process

Prior to the beginning of the investigation, all participants will be provided with a written copy of an IRB-approved consent statement. The investigator will explain the consent document to the participant and answer any questions. Participants will be told explicitly that agreement to the consent document and their participation in the investigation is entirely voluntary and may be revoked at any time for any reason or no reason.

16 Adverse events, adverse device effects and device deficiencies

Device deficiencies and all **adverse events (AE)** including all **serious adverse events (SAE)** are collected, fully investigated and documented in the source document and appropriate case report form (CRF) during the entire investigation period, i.e. from participant's informed con-sent until the last protocol-specific procedure, including a safety follow-up period (ISO-14155, 2020). Documentation includes dates of event, treatment, resolution, assessment of serious-ness and causal relationship to device and/or investigation procedure.

Information on AEs is systematically collected during the regular investigation visits, and phone calls (if applicable).

The investigator(s) will follow-up on a biweekly basis with any participant experiencing an AE until either a) the participant reports resolution of the AE or b) 8 weeks have passed since the participant's final visit. If, however, the participant's condition worsens throughout the 8 week follow-up period, the investigator will continue to follow-up biweekly until the AE is resolved or the participant's condition stabilizes over an 8 week period.

The reporting of Serious Adverse Events and Device Deficiencies follows the Regulation (EU) 2017/745 and the MDCG 2020-10/1 Safety Reporting in Clinical Investigations of Medical Devices under Regulation (EU) 2017/745.

The causality assessment of the SAE will be conducted according to MDCG 2020-10/1 Safety Reporting in Clinical Investigations of Medical Devices under Regulation (EU) 2017/745.

17 Vulnerable populations

This investigation will not include any vulnerable populations.

18 Suspension or premature termination of the clinical investigation

The clinical investigation will be suspended or prematurely terminated if the feature and/or investigative device malfunctions or if the participants or researchers are exposed to safety risks other than those outlined in this document. These events may include but are not limited to – natural disaster, widespread outbreak of illness, compromised structure of the investigation site, etc.

In accordance with the FDA, the investigation will be terminated within 5 days if there is any reason to believe the participants are exposed to an unreasonable degree of risk.

19 Publication policy

The clinical investigation will be registered in clinicaltrials.gov, a publicly accessible database, as required by U.S. regulations.

The results of the clinical investigation will be published on clinicaltrials.gov no later than one calendar year following the final participant appointment.

An internal report of the results of this investigation will be completed and uploaded to eQMS.