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Owner: ***Federica Bianchi,fedb***

Reviewed by (Name, Initials, Date, Time):

[Liselotte Borup (lsbo) 11-Feb-2020 12:43:10 CET]

Approved by (Name, Initials, Date, Time):

[Tove Helene Rosenbom (tvro) 11-Feb-2020 18:34:25 CET]

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Revision history

Revision no	*Date*	*Description*
0	16/07/19	Version 1 : version submitted to Ethics Committee
1	09/09/19	Version 2: comments from REC are addressed

Summary

Study site:	Queen Elizabeth, University Hospitals Birmingham NHS Foundation Trust; B15 2TH
Investigation code:	BC103
Principal investigators:	William Brassington, Consultant Clinical Scientist / Head of Audiology Services Audiology Department, Nuffield House, University Hospitals Birmingham Mindelsohn Way, Edgbaston, B15 2TH Birmingham United Kingdom
Coordinating investigator	N/A
Sponsor:	Oticon Medical AB Datavägen 37 B 43632 Askim Sweden
Monitor:	Oticon Medical representatives
Objective(s):	The primary objective of this study is to evaluate the decrease in pupil dilation when listening to speech-in-noise with OSN ON compared to OSN OFF at +4 dB SNR. Secondary and tertiary objectives are listed in Sec. 6.
Methodology:	Single-center, single-blinded, prospective study including three laboratory visits and a field trial period. Each participant will serve as his/her own control.
No of Patients:	30 patients are required for study completion.
Product:	Ponto 4 developed by Oticon Medical AB (Askim, Sweden) will be used for laboratory and field-trial testing. All devices and software used in this study are CE marked.

Main inclusion/exclusion criteria:	**Inclusion criteria** • Minimum 18 years and maximum 70 years old. • UK English mother tongue. • Bilateral conductive or mixed hearing loss. • Users fitted unilaterally or bilaterally on abutment. • Users are currently fitted with either Ponto 3, Ponto Plus or Ponto Pro (devices with a fitting range up to 45 dB HL). • Users with at least 6 months of daily experience with one Ponto sound processor. • BC thresholds of the implanted ear(s) better (lower) than or equal to 40 dB HL (average of 0.5, 1, 2 and 3 kHz) based on BC in-situ measurement at the first visit. • People currently employed/self-employed (since the Need for Recovery questionnaire refers to work-related fatigue). • Speech recognition scores better (higher) than or equal to 50% at +4 dB SNR with OSN OFF (as assessed via the first training list at Visit 1). This is to avoid including patients that are already "giving up" at +4 dB SNR. • Users entitled for a sound-processor upgrade (according to the investigator) will first be selected. If there are not enough users entitled for an upgrade, then patients fitted with Ponto between 7 and 12 months before visit 1 will be considered. If there are not enough users within 7-12 months, then patients fitted with Ponto between 13 and 18 months before visit 1 will be considered. **Exclusion criteria** • Single-sided deafness (SSD) • Hearing aid or cochlear implant on the opposite ear. • Test persons with current eye diseases and/or history of eye surgery on both eyes. • If the patient takes medications that can impact the autonomic nervous system – and hence pupil dilation (e.g., drugs for Parkinson's disease, peptic ulcers, incontinence, motion sickness). • If the investigator or physician assesses that the patient is not fit for trial participation.
Intervention(s) :	Patients are fitted with Ponto 4 sound processor.
Duration of study period:	Each patient will be enrolled in the study for approximately 4 months.
Criteria for safety:	No safety risk is expected.
Statistical methods:	Growth curve analysis, Mixed model ANOVA, Paired t-test / Wilcoxon signed rank test.
Investigation plan prepared by:	Federica Bianchi, Oticon Medical AB

1. Contents

1. ABBREVIATIONS

AE	Adverse Event
ANOVA	Analysis of Variance
BAHS	Bone Anchored Hearing System
CHL	Conductive Hearing Loss
CIP	Clinical Investigation Plan
CRF	Case Report Form
dB	Decibel
DFC	Dynamic Feedback Cancellation
ET camera	Eye Tracking camera
HI	Hearing Impaired
HINT	Hearing In Noise Test
HL	Hearing Loss
Hz	Hertz
MHL	Mixed Hearing Loss
OSN	OpenSound Navigator
PPD	Peak Pupil Dilation
SAE	Serious Adverse Event
SNR	Signal-to-Noise Ratio
SP	SuperPower
SPL	Sound Pressure Level
SSD	Single Sided Deafness
UCL	Uncomfortable Level

2. INTRODUCTION

The concept of listening effort has, for a long time, been difficult to quantify since it was typically assessed via questionnaires completed *after* a given task was performed. Today, several studies have shown that the pupil dilation can function as an objective indicator of listening effort *during* the execution of a task (Wendt et al., 2017; Zekveld et al., 2011; Ohlenforst et al., 2017). An eye-tracking camera can be used to measure the task-evoked pupil dilation in environments that differ in terms of listening demands. It has been shown that the pupil typically dilates as the task demands imposed by the listening situation increase (Beatty, 1982; Kahneman and Beatty, 1966). However, pupil size and task demands are not monotonically related. Pupil size follows an inverse U-shaped function of task demands, i.e., the pupil increases in size with increasing task demands up to a certain level of task demand. After this ”maximum effort” point, the pupil size decreases in size suggesting that the listener ”gives up” in the presence of a too demanding listening situation (Ohlenforst et al., 2018; Ohlenforst et al., 2017).

The focus of this study is to investigate listening effort during a speech-in-noise task, where task demands are systematically varied, in bone-anchored hearing systems (BAHS) users wearing the new bone-anchored sound processor from Oticon Medical AB (Ponto 4). The aim is to compare listening effort with different settings of Ponto 4’s new feature, called OpenSound Navigator (OSN). The OSN feature is a Multi-Speaker Access Technology that can offer different levels of benefit to fit

different users' needs. In this study, we aim to evaluate the relationship between pupil size and task demands for different OSN settings in BAHS users. Additionally, the aim of this study is to investigate the relationship between pupil dilation and acclimatization with Ponto 4. Since it is unknown whether pupillometry is a sensitive measure to reflect acclimatization to a new bone-achored device, this part of the study is completely novel and exploratory. Hence, the outcomes of this study may provide us with novel insights into listening effort in bone-anchored users, as well as acclimatization to a new sound processor and its impact on daily-life fatigue.

3. IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATIONAL DEVICE

The investigational device used in this study is Ponto 4 – the bone-anchored sound processor developed by Oticon Medical AB (Askim, Sweden), which was released in June 2019 and is CE marked.
Ponto 4 is intended for improvement of hearing for patients with conductive or mixed hearing losses, whether unilaterally or bilaterally fitted, and for those with single sided deafness. Ponto 4 is intended to be used either with the Ponto implant system or with specific compatible abutments and implants. Ponto 4 can also be used on a softband. This study will only evaluate the sound processor on already implanted BAHS users. The use of the investigational device in this study will be within Ponto 4 intended purpose.

For the fitting of Ponto 4, Genie Medical BAHS 2019.1 will be used.

The devices used in the study will be traced with serial numbers. The serial numbers of the devices together with the test person identification number will be noted in the Case Report Form (CRF).

4. PRELIMINARY INVESTIGATIONS AND JUSTIFICATION OF THE STUDY

The concepts of fatigue, cognitive load, and listening effort have received increased attention in the past years (Pichora-Fuller et al., 2016), as it has become clear that the interplay between auditory and cognitive factors has a central role in everyday listening environments. The need to consider listening effort when evaluating a listening situation has become of great importance, especially because physiological measures of effort, such as pupillometry, have been shown to provide additional information beyond behavioral performance (Zekveld et al., 2010; Wendt et al., 2017; Ohlenforst et al., 2018). Hence, considering both perceptual and cognitive factors during listening tasks can provide a powerful framework to observe complementary aspects of effortful listening.

5. RISKS AND BENEFITS OF THE INVESTIGATIONAL DEVICE AND CLINICAL EVALUATION

The investigational device (Ponto 4) is fitted on users that are already Ponto users implanted with an abutment. Additionally, Ponto 4 will be fitted according to the manufacturer recommend fitting guidelines. Hence, the risk of participating in this study is low and comparable to corresponding rehabilitation outside this study. No risks are expected in regards to using Ponto 4 as investigational device. No disadvantages are expected for the subjects, other than the tiredness the patients can experience when listening to speech in noise and having to repeat speech. Any risk of of using Ponto 4 in the patients's daily life is equal to that associated with the use of the patient's own Ponto device.

Additionally, the patient will be offerred to keep the investigational device after the completion of the study if he/she wishes to do so.

There are no expected interactions of the treatment in this study with concomitant medical treatments or medication.
Three visits (of about 2 hours each) are included in this study, which is one extra visit as compared to normal standard care for patients that are switching BAHS sound processor.
It is therefore concluded that the risks associated with participation in this study are minimal and acceptable when weighed against the potential user benefits and the gain in terms of research results in a field important for long-term patient outcomes.
All adverse events will be registered and taken into consideration when compiling the final report.

6. OBJECTIVES AND HYPOTHESES

6.1 Primary Objective and hypothesis

- The primary objective of this study is to evaluate the decrease in pupil dilation when listening to speech-in-noise with OSN ON compared to OSN OFF at +4 dB SNR. The hypothesis is that OSN ON will lead to a significant reduction in pupil dilation (i.e., less listening effort) as compared to OSN OFF.

6.2 Secondary Objectives and hypotheses

The secondary objectives of this study are:

- To evaluate the difference in peak pupil dilation (PPD) when listening to speech-in-noise with OSN ON compared to OSN OFF across SNRs. The hypothesis is that there is a significant decrease in PPD with OSN ON vs. OSN OFF at SNRs lower than 5 dB but higher than the ”give-up” point.

- To evaluate the difference in speech recognition scores with OSN ON compared to OSN OFF across SNRs. The hypothesis is that there is a significant increase in speech intelligibility with OSN ON vs. OSN OFF.

- To evaluate the change in overall pupil dilation, as calculated via Growth Curve Analysis, with OSN ON vs. OFF at different SNRs. The hypothesis is that the overall pupil dilation is significantly reduced with OSN ON compared to OSN OFF at SNRs lower than 5 dB but higher than the ”give-up” point.

- To evaluate the change in overall pupil dilation after first fitting with Ponto 4 (visits 1 or 2), as calculated via Growth Curve Analysis, with OSN Auto vs. OFF at +4 dB SNR.
- To evaluate the change in overall pupil dilation after the field-trial period with Ponto 4 (visit 3), as calculated via Growth Curve Analysis, with OSN Auto vs. OFF at +4 dB SNR.

- To evaluate the change in overall pupil dilation, as calculated via Growth Curve Analysis, with OSN Auto vs. ON at +4 dB SNR. The hypothesis is that there is no significant difference in overall pupil dilation between OSN Auto compared to OSN ON.

- To evaluate self-reported performance (via the SSQ questionnaire) with Ponto 4 after 1 month field trial compared to own device.

- To evaluate self-reported performance (via the SSQ questionnaire) with Ponto 4 after 3 months field trial compared to own device.

- To evaluate self-reported performance (via the SSQ questionnaire) with Ponto 4 at 3-months follow up compared to 1-month follow up.

- Relationship between peak pupil dilation and speech recognition scores.

- Investigate the preference of Ponto 4 compared to own device.

- Investigate aided sound field thresholds with Ponto 4 and remaining air-to-bone gap (also known as BC gain or effective gain).

6.3 Tertiary objectives

The following tertiary objectives related to acclimatization and daily-life fatigue are considered exploratory.

- To evaluate daily-life fatigue (via the Need for Recovery scale – NfR questionnaire) with Ponto 4 after field trial compared to own device.

- Relationship between NfR scores and pupil dilation with Ponto 4 after field trial.

- We will investigate in an explorative manner how the overall and peak pupil dilation change between Visit 1-2 (before the field trial) and Visit 3 (after the field trial), for the contrast OSN Auto vs. OSN OFF at +4 dB SNR. Due to the explorative nature of the tertiary objective, no hypothesis is anticipated here.
- We will investigate in an explorative manner how the pupil dilation curve changes between Visit 1-2 (before the field trial) and Visit 3 (after the field trial), for the contrast OSN Auto vs. OSN OFF at +4 dB SNR. Due to the explorative nature of the tertiary objective, no hypothesis is anticipated here.
- We will investigate in an explorative manner how the recognition scores change between Visit 1-2 (before the field trial) and Visit 3 (after the field trial), for the contrast OSN Auto vs. OSN OFF at +4 dB SNR. Due to the explorative nature of the tertiary objective, no hypothesis is anticipated here.
- Relationship between pupil dilation and the patient's PTA and characteristics.
- Relationship between speech recognition scores and the patient's PTA and characteristics.

- Relationship between NfR scores and the patient's PTA and characteristics.

7. DESIGN OF THE CLINICAL INVESTIGATION

This study is a single-center, single-blinded, prospective study on adults BAHS users, who are already experienced Ponto users (see inclusion criteria).
All participants will perform a speech-in-noise test at different SNRs and at three different Ponto 4 settings (OSN ON, OSN OFF, OSN Auto) while an eye-tracking camera records pupil dilation as an indicator of listening effort. The patients are blinded to the test condition. Patients that are bilaterally implanted, will be tested bilaterally with a Ponto 4 placed on each abutment. Patients that are unilaterally implanted will be tested with a Ponto 4 on the implanted side and the opposite ear will remain open and unaided. For the unilaterally fitted patients, no crucial contribution from the opposite side is expected to occur since they also have a hearing loss on the opposite ear (see inclusion criteria). All participants will perform all conditions and will act as their own control.
See Appendix A and B for a list of all conditions and time estimates.

Pupillometry at Visits 1 and 2

The tested conditions will be balanced across participants and across visits (see Figure 1 and Appendix B for the details). The three OSN settings (OSN ON, OSN OFF, OSN Auto) will be tested at the same visit for the same SNR to avoid differences in pupil dilation that could occur across visits (e.g., small differences in camera positioning, lighting, fatigue,..). The order of SNRs will be randomized within each OSN settings (see Figure 1). In a best attempt to maintain motivation constant within and across visits, easy and difficult conditions will be balanced across visits (i.e., SNRs of -8 dB, 0 dB, and +8 dB at one visit; SNRs of -4 dB and +4 dB at the other visit).
Two training lists (+4 dB SNR with OSN OFF, and -4 dB SNR with OSN ON) will be performed before starting the test at Visit 1. Since Visit 2 is scheduled within a week after Visit 1, only one training list will be performed before starting the test at Visit 2.
The setting OSN Auto will only be performed at +4 dB SNR. This SNR was specifically chosen to lead to a speech intelligibility performance, on average, above 50% – hence before the "give up" point, while still activating of the OSN feature. The OSN Auto condition will be tested either at Visit 1 or Visit 2, in between the other two settings (see Figure 1).

Field-trial period

After the first two laboratory visits, the test person will undergo a field trial period of about 3 months, where Ponto 4 will be used in everyday life (with OSN set to Auto) instead of the patient's own Ponto.

Pupillometry at Visit 3

After the field trial period, a third visit will be performed, where the same speech-in-noise test will be carried out at two Ponto 4 settings (OSN Auto and OSN OFF), while an eye-tracking camera records pupil dilation. Two training lists (+4 dB SNR with OSN OFF, and +4 dB SNR with OSN Auto) will be performed before starting the test at Visit 3.

The test leader will change the test devices/programs when required by the test condition (OSN ON, OSN OFF, OSN Auto) and according to the SNR randomization for each patient.

Two questionnaires (SSQ and NfR) will also be completed in relation to the patient's own device (at Visit 1) and in relation to Ponto 4 after 3-months trial (at Visit 3) In addition, the SSQ will also be completed after 1-month trial with Ponto 4. A preference questionnaire will also be completed at Visit 3 to evaluate the preference of Ponto 4 vs. the patient's own device.

Finally, audiometry (AC, masked BC) and sound-field thresholds (aided with Ponto 4) will be performed at Visit 3. These audiometric evaluations are performed at Visit 3 instead of Visit 1 to reduce the burden on the participants at Visit 1.

See the detailed study overview in Table 1.

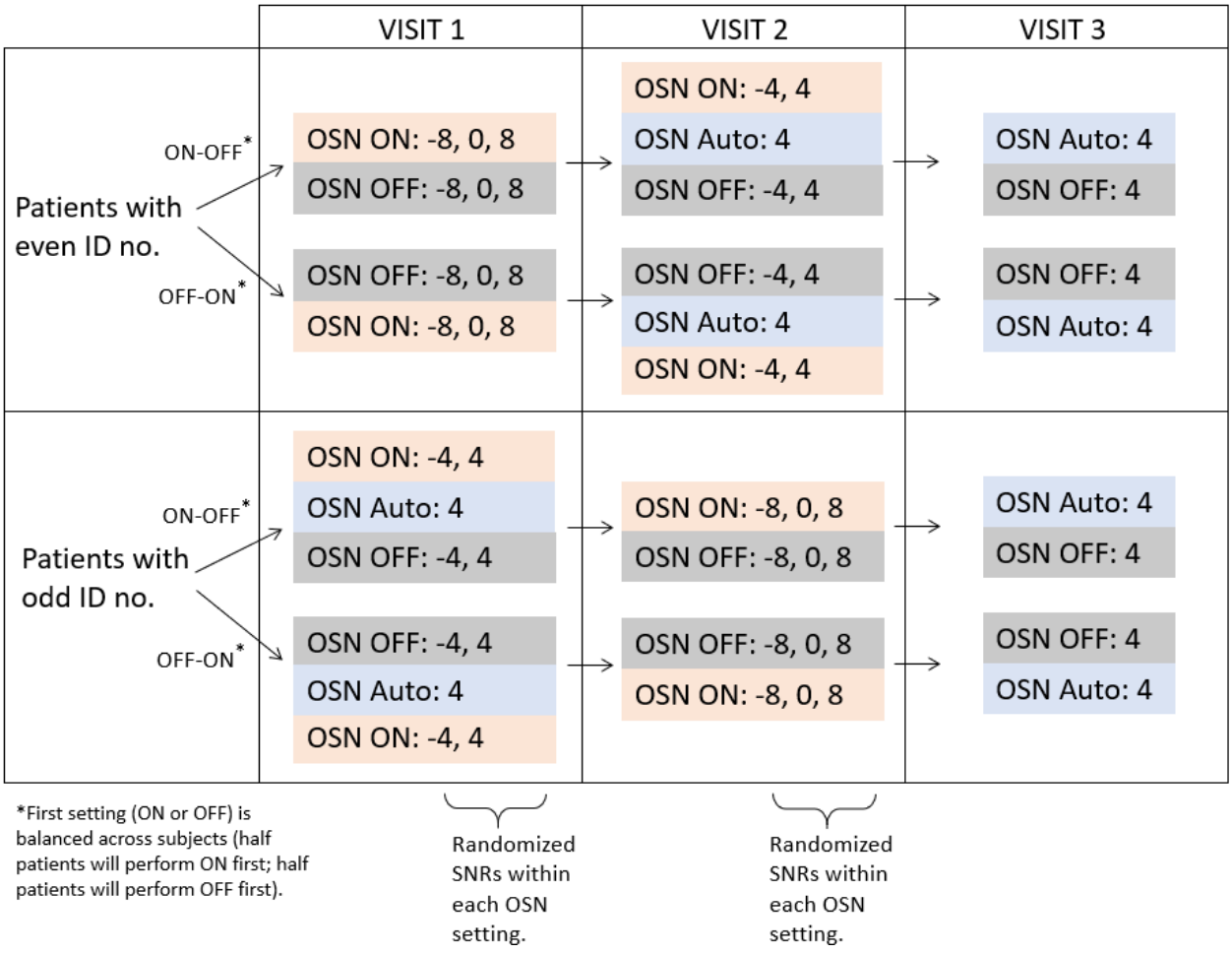

Figure 1: Schematic showing the study conditions (SNRs and OSN settings) for pupillometry testing, balanced across patients and visits.

Table 1 Overview of the study visits.

	Visit 1	*Visit 2 [1-10 days after visit 1]*	*Phone reminder [4-5 weeks after visit 2]*	*Visit 3 [12-15 weeks after visit 2]*
Consent form	*x*			

BC in situ and fitting with Ponto 4	*x*			
Pupillometry	*x*	*x*		*x*
Field trial with Ponto 4		*x (start)*		*x (end)*
Audiometry (AC and masked BC)				*x*
Sound field audiometry				*x (aided with Ponto 4)*
SSQ questionnaire	*x (reference device)*		*x (Ponto 4)*	*x (Ponto 4)*
Need of recovery questionnaire (NfR)	*x (reference device)*			*x (Ponto 4)*
Preference questionnaire				*x*

7.1. Endpoints

7.1.1 Primary endpoints

- Difference in overall pupil dilation, as calculated via Growth Curve Analysis, between OSN ON and OSN OFF at +4 dB SNR (conditions measured at visit 1 or 2).

7.1.2 Secondary endpoints

- Difference in peak pupil dilation (PPD) between OSN ON and OSN OFF across SNRs.
- Difference in speech recognition scores between OSN ON and OSN OFF across SNRs.
- Difference in overall pupil dilation, as calculated via Growth Curve Analysis, between OSN ON and OSN OFF across SNRs.
- Difference in overall pupil dilation between OSN Auto and OSN OFF at +4 dB SNR (measured at visits 1 or 2), as calculated via Growth Curve Analysis.
- Difference in overall pupil dilation between OSN Auto and OSN OFF at +4 dB SNR (measured at visit 3), as calculated via Growth Curve Analysis.
- Difference in overall pupil dilation between OSN Auto and OSN ON at +4 dB SNR (measured at visits 1 or 2), as calculated via Growth Curve Analysis.
- Difference in SSQ scores between Ponto 4 after 1 month field trial and own device.
- Difference in SSQ scores between Ponto 4 after 3 months field trial and own device.
- Difference in SSQ scores between Ponto 4 after 1-month field trial and after 3-months field trial.

- Correlation between peak pupil dilation and speech recognition scores.

- Number of test subjects preferring Ponto 4.
- Sound scenarios for which test subjects significantly prefer Ponto 4 over own device.
- Difference in dB between aided thresholds and BC in-situ thresholds –i.e., remaining air-bone gap (also known as BC gain or effective gain).

7.1.3 Tertiary endpoints

- Difference in NfR scores with Ponto 4 after field trial and own device.

- Correlation between NfR scores and pupil dilation with Ponto 4 after field trial.
- Difference in overall pupil dilation (intercept term) between Visit 1-2 and Visit 3 for the contrast OSN Auto vs. OSN OFF.
- Difference in peak pupil dilation between Visit 1-2 and Visit 3 for the contrast OSN Auto vs. OSN OFF.
- Difference in the following parameters between Visit 1-2 and Visit 3 for the pupil curves obtained with OSN Auto and OSN OFF: rate of growth/decay (linear term), changes in the rate of growth/decay (quadratic term), and the steepness of the curve around inflection points (cubic term).
- Difference in speech recognition scores between Visit 1-2 and Visit 3 for OSN Auto and OSN OFF.
- Correlation between pupil dilation and the patient's PTA and characteristics (e.g., age, unilateral/bilateral implantation).
- Correlation between speech recognition scores and the patient's PTA and characteristics (e.g., age, unilateral/bilateral implantation).
- Correlation between NfR scores and the patient's PTA and characteristics (e.g., age, unilateral/bilateral implantation).

7.2. Outcome measures

7.2.1 Test subject characteristics

The following patient characteristics will be recorded:

- Gender (Female, Male, No answer)
- Age
- Unilateral or bilateral BAHS surgery and side
- Date of first BAHS fitting on abutment (year)
- Name of current bone anchored sound processor
- Date of first fitting with current own bone anchored sound processor ([mm/yy])
- History of eye surgery (if any, which eye and year)
- Dominant or preferred eye (Left, Right, None, Not known)
- Job at visit 1 and 3, and whether it is the same.

7.2.2 Primary outcome measures

- Overall pupil dilation for OSN ON and OSN OFF at +4 dB SNR (intercepts obtained from Growth Curve Analysis).

7.2.3 Secondary outcome measures

- Pupil dilation.
- Growth Curve Analysis parameters.
- Speech recognition scores.
- SSQ questionnaire scores.
- Preference questionnaire scores.
- Aided sound field thresholds.
- BC in situ thresholds.

7.2.4 Tertiary outcome measures

- Pupil dilation.
- Growth Curve Analysis parameters.
- Speech recognition scores.
- Need for Recovery (NfR) questionnaire scores.
- BC in situ thresholds (PTA).
- Patient's characteristics.

7.3. Investigational device(s) and comparators

This is a post market study and the devices used in this study are CE marked. The test subjects' own devices will only be used as a reference device for the questionnaires (SSQ, NfR, preference). For the laboratory testing and for the field-trial period, Ponto 4 sound processors will be used. The following devices (and item numbers) will be used:

Name	Amount	Part number (color)	Description
Ponto 4	60	186777 (CBE) 186778 (TC) 186779 (SIL) 186780 (STG) 186781 (CNB) 186782 (DBL)	*Oticon Medical BAHS Sound Processor. Released in 2019.*

7.3.1. Concomitant treatment and medication

Medication which is considered necessary for the patient's safety and well-being may be given at the discretion of the investigator. Only medication for adverse events must be recorded in the

appropriate section of the Case Report Form (CRF).

7.4 Subject population

Based on the sample size calculation reported in Sec. 12, it was decided that a total of 30 patients will be included in the study. The patients will be selected from the Queen Elizabeth Hospital database. A member of the clinical team at the hospital will perform a pre-screening by looking at the patient's journal, according to the inclusion criteria listed below. It was decided to include preferably patients that are entitled for a sound processor upgrade to reduce the burden on the patient, since patients entitled for an upgrade would need to visit the clinic anyways to get a new sound processor fitted. Only the patients that fulfil those inclusion and exclusion criteria that are available on the patient's journal will be contacted and considered suitable candidates for the study. Screening will occur at Visit 1 after the informed consent is signed. Patients that fulfil all inclusion and exclusion criteria will be enrolled in the study.

Inclusion criteria

- Minimum 18 years and maximum 70 years old.
- UK English mother tongue.
- Bilateral conductive or mixed hearing loss.
- Users fitted unilaterally or bilaterally on abutment.
- Users are currently fitted with either Ponto 3, Ponto Plus or Ponto Pro (devices with a fitting range up to 45 dB HL).
- Users with at least 6 months of daily experience with one Ponto sound processor.
- BC thresholds of the implanted ear(s) better (lower) than or equal to 40 dB HL (average of 0.5, 1, 2 and 3 kHz) based on BC in-situ measurement at the first visit.
- People currently employed/self-employed (since the Need for Recovery questionnaire refers to work-related fatigue).
- Speech recognition scores better (higher) than or equal to 50% at +4 dB SNR with OSN OFF (as assessed via the first training list at Visit 1). This is to avoid including patients that are already "giving up" at +4 dB SNR.
- Users entitled for a sound-processor upgrade (according to the investigator) will first be selected. If there are not enough users entitled for an upgrade, then patients fitted with Ponto between 7 and 12 months before visit 1 will be considered. If there are not enough users within 7-12 months, then patients fitted with Ponto between 13 and 18 months before visit 1 will be considered.

Exclusion criteria

- Single-sided deafness (SSD)
- Hearing aid or cochlear implant on the opposite ear.
- Test persons with current eye diseases and/or history of eye surgery on both eyes.
- If the patient takes medications that can impact the autonomic nervous system – and hence pupil dilation (e.g., drugs for Parkinson's disease, peptic ulcers, incontinence, motion sickness; Winn et al. (2018)).
- If the investigator or physician assesses that the patient is not fit for trial participation.

Please note that if a patient has taken any caffeine (e.g., coffee, tea, energy drink, other) in the 6 hours preceding testing, the visit should be rescheduled.

Criteria for early termination during the study

- System not being able to track pupil dilation (e.g., technical failure, eye iris color, other).
- Noisy pupil recordings (e.g., too many eye blinks, elevated baseline, not possible to individuate a clear peak dilation because of an event-unrelated dilation occurring at baseline, ..).
- If the patient cannot remove (or is uncomfortable to be tested without) glasses or contact lenses during pupillometry and the system cannot track the pupil reliably.
- Inability to complete the speech-in-noise test.
- Patient who switch to non-Ponto sound processor during the field-trial period.
- Patients who do not want to continue to participate.
- If the patient start taking medications that can impact the autonomic nervous system – and hence pupil dilation (e.g., drugs for Parkinson's disease, peptic ulcers, incontinence, motion sickness; Winn et al. (2018)).
- If the test leader or physician assesses that the patient is not fit for trial participation at any stage.

If a patient is excluded or early terminated from the study or decides to withdraw from the study, the patient will continue to receive care from the physician following the clinical practice guidelines of the hospital.

Procedure for replacement of subjects

If test persons are withdrawn from the study, the recruitment process will continue until 30 patients have completed Visit 1 and Visit 2. Dropouts will be replaced during the study by enrolling new test participants.

Time frame for the study

The study is a 4 months study, i.e. 4 months is the total time a patient is enrolled in the study. The second visit is expected to be performed within maximum 10 days after Visit 1. The second visit cannot be performed on the same day as Visit 1. Hence, the time window for Visit 2 is 1-10 days after Visit 1. The third visit is expected to be performed 3 months after Visit 2. The time window for Visit 3 is 12-15 weeks after Visit 2 to allow for investigation of acclimatization.

The data after completion of the first two visits may be analyzed and reported if the investigator finds this appropriate. Interim data analysis will be performed in November 2019 to be able to present interim results at the OSSEO conference in December 2019.
Enrollment will start after receiving Ethical approval and will be ongoing until the total number of patients (see Sec. 12) has been reached. This is expected to be fulfilled by the end of January 2020. The end of the study is therefore expected to occur by the end of May 2020.
After the study, the patient will be receiving follow-up according to the clinic's standard procedures for patients with BAHS.

8. STUDY PROCEDURES

8.1. Investigation outline

Each test person will participate in three lab visits and a field-trial period.

Pre-screening

Adult patients who are already implanted with a BAHS are considered candidates for the study (see inclusion criteria).

- The audiologist will pre-screen the database for suitable candidates that meet the inclusion criteria.
- The test person is contacted over the phone or through an email or letter.
- The test person is informed about the study.
- The test person is given time to consider his/her participation and ask questions.
- The test person is given the opportunity to either accept or decline the offer to participate in the study.
- If a test person accepts, the 1st visit is scheduled. The patient is reminded that no caffeine should be taken on the 6 hours before Visit 1.

Visit 1

- The test person is informed about the study including all study related visits.
- Detailed information and instructions about the study.
- Consent form is signed.
- The test person's demographical data as well as their personal data and patients' characteristics are registered in the CRF.

- Fitting of Ponto 4 is performed (OSN ON, OSN OFF, OSN Auto)
- Pupillometry during a speech-in-noise test is performed (training, OSN ON, OSN OFF, OSN Auto – see Figure 1).
- All subjects fill in the SSQ and NfR questionnaires in relation to their own device (reference device).

Visit 2: 1-10 days after Visit 1

- Get Ponto 4 ready for testing (OSN ON, OSN OFF, OSN Auto)
- Pupillometry during a speech-in-noise test is performed (training, OSN ON, OSN OFF, OSN Auto – see Figure 1).
- The test person is instructed on the usage of Ponto 4 (including getting the Oticon ON app on their smartphone, or offer a Connectclip)
- SSQ questionnaire is handed out.

Phone reminder: 4-5 weeks after Visit 2

- The test leader reminds the patient to fill out the SSQ questionnaire in relation to the performance with Ponto 4 in the first month of trial. The patient will then put the questionnaire in an envelope and bring it at Visit 3.

Visit 3: 12-15 weeks after Visit 2

- Hand in SSQ questionnaire filled out at home.
- Pupillometry during a speech-in-noise test is performed (training, OSN OFF, OSN Auto).
- Audiometry is performed (AC, masked BC).
- Sound-field audiometry is performed with Ponto 4.
- All subjects fill in the SSQ and NfR questionnaires in relation to Ponto 4.
- All subjects fill in the preference questionnaire.

8.2. Clinical assessments

8.2.1. *Pure tone audiogram*

Detection of pure tones delivered by the audiometer via air-conduction and bone conduction, as used for measuring conventional audiometry. Tested frequencies for air-conduction are: 250 Hz, 500 Hz, 750 Hz, 1 kHz, 2 kHz, 3 kHz, 4 kHz, 6 kHz, 8 kHz. Tested frequencies for bone-conduction are: 500 Hz, 1 kHz, 2 kHz, 3 kHz, 4 kHz.

8.2.2. *Sound field audiometry*

Aided threshold will be measured in order to calculate remaining air-to-bone gap (also called BC gain or effective gain).

The Ponto 4-45 will be programmed with DFC OFF, directionality mode Omni and noise reduction OFF.
The measurement will be conducted in a sound field setup with the loudspeaker placed 1 meter in front of the test person (0° azimuth), with warble tones at frequencies 250-, 500- 750-, 1000-, 1500-, 2000-, 3000-, 4000-, 6000- and 8000 Hz.

8.2.3 Fitting

Fitting will be performed by a trained audiologist at Queen Elizabeth Hospital. The fitting will follow the recommended fitting flow from the manufacturer. The Ponto 4 will be fitted with the NAL-NL1 rationale; a feedback measurement as well as a BC in-situ audiometry measurement will be conducted. Further and individualized fine tuning will not be performed, for comparison reasons, unless it is absolutely necessary. See Table 2 for an overview of the settings for each condition: OSN ON, OSN OFF, OSN Auto.

Table 2 Overview of Ponto 4-45 settings for OSN ON, OSN OFF, OSN Auto.

	OSN ON	OSN OFF	OSN Auto
Feedback measurement	X	X	X
DFC	As prescribed	As prescribed	As prescribed
BC in-situ audiometry	Copied from OSN Auto	Copied from OSN Auto	X

Fine tuning	No fine tuning	No fine tuning	Preferably no fine tuning
OpenSound Navigator: **-Directionality settings** **-Open Sound transition**	Full Directional Very High*	Omni N/A	Open Automatic Medium
Noise reduction complex	-9 dB	OFF	-7 dB (default)
Noise reduction simple	-3 dB	OFF	0 dB (default)

*When fitting the 'OSN ON – condition' the following steps will be followed:

1. Directionality settings will be set to Open Automatic;
2. Transition will be set to Very High;
3. Directionality settings will be set to Full Directional.

8.3. Test setup and materials

8.3.1 Pupillometry

The setup for this study consists of five loudspeakers positioned at a distance of 1 m from the test participant (see Figure 1). An eye tracking camera will be placed in front of the test person approximately 60 cm from the eyes. The eye-tracking camera is the Pupil Labs. The camera will track the pupil size of the test person during the speech-in-noise task.

UK English sentences will be presented in a 4-talker babble background noise. The loudspeaker at the 0° azimuth position will playback the target speech signal. The remaining 4 loudspeakers will each playback one of the 4 overlapping babble talkers at +/-90° and +/-150° azimuth. Additionally, unmodulated speech-shaped noise (SSN) was added to the 4-talker babble to simulate a diffuse noise environment and to trigger the automatic control of the NR algorithms (as in Wendt et al., 2017). The SSN was added to the two competing talkers presented from the back at ±150° with an SNR of −1.8 dB (i.e., the SSN was presented at a lower level than the babble).

Each trial will start with a short silence, followed by a baseline with noise (see silence and baseline durations in Appendix A). The sentence will start after the baseline. After sentence offset, the participant will need to wait for 3 seconds before repeating the sentence (retaining window).

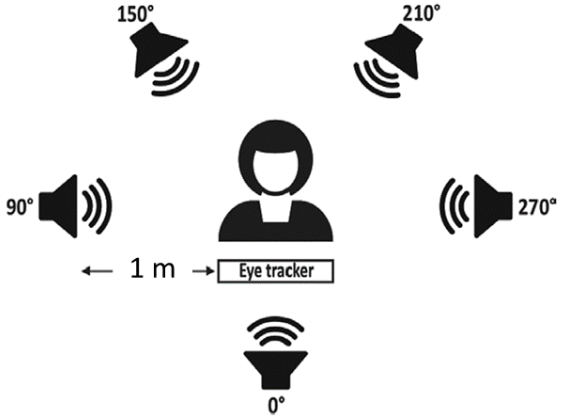

Figure 2 Loudspeaker and camera setup used for the speech-in-noise test. The participant will wear one or two Ponto 4 on abutment.

8.3.2 Speech recognition test

Speech recognition scores (% correct) will be measured for the speech-in-noise task over a broad range of SNRs from -8 dB to +8 dB. See the details of the target sentences and noise in the previous section. The overall masker level (4-talker babble and SSN) is kept constant at 70 dB SPL to ensure that the noise would not become too loud at low SNRs. The level of the speech is adjusted consequenctly for each tested SNR.

8.3.3 Speech, Spatial, and Qualities of Hearing (SSQ) questionnaire

The Speech, Spatial and Qualities of Hearing Scale (SSQ) is designed to measure a range of hearing disabilities across several domains (Gatehouse and Noble, 2004). Particular attention is given to speech perception in a variety of competing contexts, and to the directional, distance and movement components of spatial hearing. In addition, the abilities both to segregate sounds and to attend to simultaneous speech streams are assessed, reflecting the reality of hearing in everyday life. Qualities of hearing experience include ease of listening, and the naturalness, clarity and identifiability of different speakers, different musical pieces and instruments, and different everyday sounds. Appendix 2 in Gatehouse and Noble (2004) gives the complete text of each item. Each item is scored from 0 to 10, with larger values always indicating greater ability.

8.3.4 Need for Recovery (NfR) questionnaire

The NFR questionnaire was originally designed and validated in Dutch and then translated into UK English (van Veldhoven and Broersen, 2003; de Croon et al., 2006). The NFR scale is an 11-item scale assessing the effects of fatigue caused by work (e.g., ” I find it hard to relax at the end of a working day”). Possible responses are “yes” or “no”. The total NFR score is the number of “yes” responses divided by the total number of items, presented as a percentage (i.e., range 0–100). The higher the score, the greater the NfR felt by the respondent.

It has been shown that a negative correlation exists between NfR scores and peak pupil dilation (Wang et al., 2018), suggesting that fatigued individual allocate less effort to perform a speech recognition in noise task. In this study, NfR will be collected in relation to both the reference device and Ponto 4, in an attempt to gain more insights into interindividual differences in PPD and factors

influencing acclimatization.

8.3.5 Preference questionnaire

The Preference questionnaire evaluates the preference for test device (Ponto 4) and reference device (own Ponto device) in different sound scenarios, for example: speech-intelligibility in quiet, speech-intelligibility in background noise in small and bigger groups. The questionnaire uses a comparative scale, where users rate whether they prefer: ”The reference device much better”, ” The reference device somewhat better”, ”No preference”, ” The test device (Ponto 4) somewhat better”, ” The test device (Ponto 4) much better”.

9. MONITORING PLAN

During the investigation representatives from Oticon Medical will have regular contacts with the investigation site. Authorized representatives of the sponsor and/or regulatory authority and/or independent ethics committees may visit the centre to perform audits/inspections, including source data verification. The extent of the monitoring will be outlined in a study specific monitoring plan.

10. INVESTIGATION ADMINISTRATIVE STRUCTURE

In this sponsor initiated study, Oticon Medical AB is the sponsor.

10.1 Information to be supplied to the clinical investigator

Before initiating the clinical investigation, the clinical investigator will receive written study and device related information, as well as being trained in the study procedure etc. The devices used in this study are already a CE marked product. If the investigator needs additional material about the device that is not covered in the product information and use materials, Oticon Medical will oblige to the request and provide as much information as possible.

10.2 Agreement between the clinical investigator and Oticon Medical

A contract between Oticon Medical and the investigators will be agreed upon for the terms of performing this study. The investigators/clinics will be given access to the equipment needed to perform measurements specific to the study.

The investigators and their clinics receive no other compensation from Oticon Medical besides what has been agreed upon in the study contract and have no further economic interest in the project other than what has been stated above.

The participants of the study will be reimbursed for the travel expenses and will not receive further compensation.

10.3 The patient’s medical record

The patient’s participation in the clinical investigation will be reported in the patient’s medical record along with patient code, title of the investigation and investigation code. All diagnoses of

relevance for the investigation, all patient visits, including those that only are relevant for the clinical investigation and all adverse events shall also be documented. It will also be documented that the patient has been informed about the study and that the patient has signed the informed consent form. The date of inclusion into the study will be recorded together with the study code. The date when the patient leaves the study will be recorded.

10.4 Data handling

All data concerning trial subjects is protected under the Act on Processing of Personal Data, the Health Act, and the EU General Data Protection Regulation (GDPR) and will be handled accordingly. All information about the subjects is under professional secrecy. All information about the subjects outside the clinic will be anonymized and the subjects' identity will not be known for anyone outside the clinic.

10.5 Suspension or premature termination of the clinical investigation

If the investigation is terminated prematurely or suspended, the sponsor will promptly inform the clinical investigation center of the termination or suspension and the reason(s) for this. The ethics committee will also be informed promptly in writing and provided with the reason(s) for the termination or suspension by the sponsor. The sponsor may at any time terminate the clinical investigation due to circumstances related to the product or company that preclude ongoing patient treatment.

11. DATA MANAGEMENT

Data captured will be recorded in the electronic Case Report Forms (eCRF), as well as on the test computer. All data must be accurately recorded in the eCRF. A source data verification list will be agreed on for data verification. A paper version of the CRF (worksheet) will be made available to be used for recording source data. The site will store the paper CRF; the sponsor may request a copy for remote monitoring. Other sources such as patient chart will also be used as source data. All patients will be given a code and should not have names and other personal identification information on eCRFs/CRF to make sure that the patient's identity remains unknown to external parties such as the Sponsor and auditor. It is the responsibility of the investigator to make sure that patient identification listings with patient code and identity are kept in a separate location than the participant folder. Personal information shall be securely stored by the site for 5 years after the study has been completed. The research data (nonidentifiable) will be kept for 20 years after the completion of the study.

11.1 Data Entry and Management

Data entry to the eCRF (online system: Smart Trial) will be performed by the investigator and the study team. Data handling, data cleaning and statistics will be performed by Oticon Medical AB or external parties such as a CRO or a statistician whom Oticon Medical AB may have a contract with for assistance. In case of the external party being contracted for data management, this organization may, as needed, gather advice from an independent clinical specialist.

11.1.1 Data management procedures, if done

Once all the data has been entered and has been reviewed by the monitor/clinical trial manager/data manager with all the pending information about the missing data satisfactorily explained, database lock will be agreed by clinical trial manager and/or data manager, principal investigator, and study project leader in a clean file meeting before any data analysis.

11.1.2 Confidentiality

At all times throughout the clinical investigation confidentiality will be observed by all parties involved. All data will be secured against unauthorized access. The principal investigator will provide direct access to source data during and after the clinical investigation for monitoring, audits, EC review and regulatory authority inspections. Permission for direct access to source documents from the subject, hospital administration and national regulatory authorities shall be obtained by the principal investigator, as per national regulations, before starting the clinical investigation.

12. STATISTICAL CONSIDERATIONS

The analysis of the primary endpoint will be performed via Growth Curve Analysis (Mirman, 2014) to compare the overall pupil dilation for OSN ON vs. OFF at +4 dB SNR. Growth Curve Analysis will also be used to evaluate differences in overall pupil dilation between OSN ON and OSN OFF at different SNRs, between OSN Auto and OSN OFF (before and after field trial), and between OSN Auto and OSN ON at +4 dB SNR.

Additionally, a mixed-model ANOVA (SNR and OSN setting as fixed factors; subject as random factor) will be used to analyze the peak pupil dilation (PPD) across SNRs. Only data of those patient that completed both Visit 1 and Visit 2 will be included in the final analysis. When applicable, post-hoc analysis will be performed via contrasts of least-square means to clarify at which SNRs the effect of OSN is significant (the p-values will be corrected for multiple comparisons using the Tukey method).

A mixed-model ANOVA (SNR and OSN setting as fixed factors; subject as random factor) will also be used to analyze the speech recognition scores across SNRs. When applicable, post-hoc analysis will be performed via contrasts of least-square means to clarify at which SNRs the effect of OSN is significant (the p-values will be corrected for multiple comparisons using the Tukey method).

A mixed model ANOVA will also be used to analyze the SSQ scores for Ponto 4 vs. own device, as well as for Ponto 4 at 1-month follow up vs. 3-months follow up.

A paired t-test or Wilcoxon sign-rank test will be used to compare the NfR scores with Ponto 4 compared to own device. Pearson's or Spearman's correlation between NfR scores and pupil dilation with Ponto 4 after field trial will be performed.

A Wilcoxon sign-rank test (two tailed) will be performed for each item of the preference questionnaire to test whether the distribution of the scores is significantly different than "No preference".

On all tests a significance level of 5% will be adopted. Correction for multiple comparisons will be performed where applicable.

12.1 Sample size calculation

The sample size calculation was based on the primary endpoint. The effect size was estimated based on the interim results of a pilot study conducted internally at Oticon Medical (Denmark) - internal study reference: BC102 - where the experimental setup was the same as in the current study. Although the speech target consisted of Danish sentences (HINT; Nielsen and Dau, 2011) instead of UK English sentences as in the current study, we expect a similar effect size. Hence, an effect size of 0.48 was estimated based on the mean and standard deviations obtained for N = 20 subjects at an SNR of +4 dB (Mean with OSN ON = 0.078; Mean with OSN OFF = 0.11; standard deviation with OSN ON = 0.09; standard deviation with OSN OFF = 0.08). These mean peak pupil dilations are in line with the results obtained in a previous study that used similar setup and conditions – although the patients wore hearing aids instead of BAHS (Wendt et al., 2017). Using a significance level of 0.05 and a statistical power of 0.8, a minimum sample size of 29 subjects was obtained. Hence, it was decided that 30 subjects should complete the primary endpoint (Visit 1 and Visit 2). If test persons are withdrawn from the study, the recruitment process will continue until 30 patients have completed Visit 1 and Visit 2.

13. AMENDMENTS TO THE CIP

In case of changes to the clinical trial protocol are needed, an amendment should be made. Proposed amendments to the CIP shall be agreed upon between the sponsor and principal investigator, or the coordinating investigator. Substantial amendments should be approved by the ethical committee before incorporated.

14. DEVIATIONS FROM CLINICAL INVESTIGATION PLAN

The investigator should not deviate from the clinical investigational plan except if needed to protect the rights, safety and well-being of the subjects. Such cases should be documented and reported to the EC and the Sponsor as soon as possible.

If deviations (other than mentioned above) occur, the Investigator should inform the monitor/clinical study manager and record in the protocol deviation log provided in the study site file. The implications of the deviation must be reviewed and discussed between the Sponsor and the Investigator. If deviations are found during monitoring visits, they should also be documented in the monitoring report and handled as above. This should be done as soon as possible after detection to avoid repetitive deviations. Continuous review of protocol deviations during monitoring visits aim to detect systematic errors and to identify retraining needs at the site. Frequency of monitoring is described in the monitoring plan and should be increased if systemic deviations are identified.
All protocol deviations must be documented stating the reason, date, the action(s) taken, and the impact for the subjects and/or the study.
If serious or repeated deviations occurs, the Sponsor has the right to initiate early termination of the study.

At the end of the study, protocol deviations will be categorized as minor or major and their consequence on analysis populations will be decided.

15. Device Accountability – if applicable

The device used in the study (Ponto 4) is a CE marked device. In total, sixty devices will be shipped to the investigation site by Oticon Medical AB. The records for the device shipping will be stored in the Trial Master File. The serial number of the sound processors that will be fitted for each patient and used throughout the study will be noted in eCRFs. Any deficiencies related to the devices will be handled through the complaint system.

16. Statements of compliance

The clinical investigation will not be commenced until approval from an ethical committee and HRA has been received.

Ethical conduct of the investigation

The clinical investigation will be performed in consistency with the current version of the declaration of Helsinki (Seventh Revision 2013), and Good Clinical practice - ISO 14155 and applicable regulatory requirements.

Ethics review

The investigation plan, including the final version of the Patient Information and Consent Form must be approved in writing by an Independent Ethics Committee (IEC) before enrolment of any patient into the investigation. Substantial amendments to the Clinical Investigation Plan must be approved by the IEC if they influence the risk for the subject. Non-substantial amendments will be notified to the ethics committee.

17. Informed consent process

The clinical investigator will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risks and benefits involved. Patients must be notified that they are free to discontinue participation in the investigation at any time. The patient will be given time for consideration and the opportunity to ask questions before signing the informed consent form. The patient signed informed consent must be obtained before conducting any procedures specifically for the investigation.
If any new information becomes available during the course of the trial that could influence the patients' willingness to participate, the patient will be informed and asked to sign a revised informed consent.

The patient will consent in writing that the results obtained in the investigation may be used in authority assessment or submissions for publications in scientific journals with the condition that privacy and confidentiality is preserved. The patient will also consent in writing that concerned personnel, sponsor representatives and regulatory authorities may have access to the patient's medical record to perform source data verification.

The signed original of the consent form must be filed by the clinical investigator. A copy of the

Patient Information including the signed consent form should be given to the patient.

18. ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES

18.1 Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device.

Adverse Events will be logged in the EDC system (Smart Trial), together with an assessment by the investigator, and reported as per below. AEs will be reported from the enrolment in the study. Any AEs occurring before then will be part of the subject's medical history.

NOTE 1: This definition includes events related to the investigational device or the comparator.
NOTE 2: This definition includes events related to the procedures involved.
NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices.

The investigator shall provide adequate medical care to a subject during and after a subject's participation in a clinical investigation in the case of adverse events, as described in the informed consent.

18.2 Serious Adverse Event (SAE)

Adverse event that:
a) led to a death, injury or permanent impairment to a body structure or a body function.
b) led to a serious deterioration in health of the subject, that either resulted in:
- a life-threatening illness or injury, or
- a permanent impairment of a body structure or a body function, or
- in-patient hospitalization or prolongation of existing hospitalization, or
- in medical or surgical intervention to prevent life threatening illness
c) led to foetal distress, foetal death or a congenital abnormality or birth defect.

NOTE 1: Planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered a serious adverse event.

18.3 Device deficiency

Inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer. Device deficiency's will be logged in the EDC system (Smart Trial) together with an assessment by the investigator, in the Device deficiency's log and reported as per 18.7 and 18.8 where applicable.

18.4 Adverse Device Effect (ADE)

Adverse event related to the use of an investigational medical device.

NOTE 1- This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.
NOTE 2- This includes any event that is a result of a use error or intentional abnormal use of the investigational medical device.

18.5 Serious Adverse Device Effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

18.6 Unanticipated Serious Adverse Device Effect (USADE)

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

NOTE: Anticipated SADE (ASADE): an effect which by its nature, incidence, severity or outcome has been previously identified in the risk management process as per ISO14971.

18.7 Reportable Events

In accordance with the applicable regulatory guidelines and directives, the following events are considered reportable events;
- any SAE,
- any Device Deficiency that might have led to a SAE if:
a) suitable action had not been taken or
b) intervention had not been made or
c) if circumstances had been less fortunate
- new findings/updates in relation to already reported events.

Reportable events shall be reported to the sponsor using the applicable forms as per timelines stated under 18.8.3.

Emergency contact for reporting SAEs and/or SADEs
Oticon Medical
Datavägen 37,
SE-436 32 Askim, Sweden
Vigilance number: +46 31 748 61 70
Mail: QA@oticonmedical.se

18.8 Reporting Timelines

18.8.1 Reports to the National Competent Authority

The sponsor is responsible to report to applicable competent authorities according to national regulations. All reportable events as described in 18.7 which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other

patients/subjects, users or other persons or a new finding to it: **immediately, but not later than 2 calendar days** after awareness by sponsor of a new reportable event or of new information in relation with an already reported event.
- any other reportable events as described in 18.7 or a new finding/update to it: **immediately, but not later than 7 calendar days** following the date of awareness by sponsor of the event.

The investigator is responsible to report to regulatory authorities regarding serious adverse events and device deficiencies that could have led to a serious adverse device effect, as required by the national regulations. Further, the sponsor is responsible to inform regarding any new significant information about the clinical investigation to the CA.

18.8.2 Reports to the ethical committee

The investigator is responsible to report to the EC serious adverse events and device deficiencies that could have led to a serious adverse device effect.

18.8.3 Report by the investigator to the sponsor

Reportable events should be reported to Oticon Medical **within 24 hours** from when Investigator is first made aware of the event using reportable events forms. It is the responsibility of the investigator to supply the sponsor, upon sponsor's request, with any additional information related to the safety reporting of an event without unjustified delay.

19. PUBLICATION POLICY

This study will be registered on ClinicalTrials.gov.

The investigator is free, and is encouraged, to publish the data from the study at scientific conferences and publications. For completion of these publications, the investigators will be primarily responsible, and Oticon Medical will assist the investigators in the process. No publications will be made without the final approval of the sponsor. Privacy and confidentiality of information about each subject will be preserved in the report and any publication of the clinical investigation data.

Oticon Medical will have the right to collect the data, and, if applicable, compare results with similar studies from other centres and publish such aggregated analyses. No publications will be made without the final approval of the investigators.

20. RESULTS AND REPORTS

When the clinical investigation is completed, even if prematurely terminated, a final report will be compiled.

The agreement on publication will be specified in the contract.

21. SIGNED AGREEMENTS

a. Sponsor

On behalf of Oticon Medical AB I agree to the terms of this investigation plan.

Date and signature:

Name and title

b. Principal Investigator

I agree to the terms of this investigation plan. I will conduct the investigation according to the procedures specified herein and in consistency with the current version of the declaration of Helsinki and ICH Guideline for Good Clinical Practice (GCP).

Date and signature:

Name and title

22. BIBLIOGRAPHY

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APPENDIX A: ALL TEST CONDITIONS

It is estimated that testing one list will take about 8 minutes. For time estimate per person/ visit please see appendix B.

Condition	Visits 1	Visit 2	Visit 3	SNRs [dB SNR]	Total no. lists	Baseline [s]	Estimated time [min]
Training lists 1	X		X	+4 (OSN OFF) -4 (OSN ON)	2	Silence: 3 s Noise: 3 s	16
Training list 2		X		+4 (OSN OFF)	1	Silence: 3 s Noise: 3 s	8
OSN OFF	X	X		-8, -4, 0, +4, +8	5	Silence: 3 s Noise: 3 s	40
OSN ON	X	X		-8, -4, 0, +4, +8	5	Silence: 3 s Noise: 3 s	40
OSN Auto	X	X	X	+4	1	Silence: 2 s Noise: 6 s	8
OSN OFF			X	+4	1	Silence: 2 s Noise: 6 s	8

APPENDIX B: BALANCED DESIGN ACROSS VISITS AND TIME ESTIMATE

VISITS 1 and 2

- Subjects with **even ID number**, will perform
  Visit 1 as follows:
  - 2 training lists
  - 6 test lists

  Hence, 8 lists will be tested in total for a total testing time of 64 minutes. About 1 h 25 min should be taken into account to conduct pupillometry at Visit 1 (including breaks).

  Visit 2 as follows:
  - 1 training lists
  - 5 test lists

  Hence, 6 lists will be tested in total for a total testing time of 48 minutes. About 1 h 05 min should be taken into account to conduct pupillometry at Visit 2 (including breaks).

- Subjects with **odd ID number**, will perform
  Visit 1 as follows:
  - 2 training lists
  - 5 test lists

  Hence, 7 lists will be tested in total for a total testing time of 56 minutes. About 1 h 15 min should be taken into account to conduct pupillometry at Visit 1 (including breaks).

  Visit 2 as follows:
  - 1 training lists
  - 6 test lists

  Hence, 7 lists will be tested in total for a total testing time of 56 minutes. About 1 h 15 min should be taken into account to conduct pupillometry at Visit 2 (including breaks).

Visit 1 (even ID no.); Visit 2 (odd ID no.)										
	OSN ON					OSN OFF				
SNRs (dB)	-8	-4	0	4	8	-8	-4	0	4	8
Training (fixed order)		X*							X	
Test -8,0,8 (Randomized order)	X		X		X	X		X		X

* Only to be performed at Visit 1

Visit 1 (odd ID no.); Visit 2 (even ID no.)											
	OSN ON					OSN Auto	OSN OFF				
SNRs (dB)	-8	-4	0	4	8	4	-8	-4	0	4	8
Training (fixed order)		X*								X	
Test -4, 4 (Randomized order)		X		X		X		X		X	

* Only to be performed at Visit 1

Additionally, the following applies:

- The first OSN setting (ON or OFF) at visit 1 and 2 will be balanced between subjects (50% of the subjects will start with OSN ON and 50% of the subjects will start with OSN OFF – see Figure 1).
- The presentation order of SNRs will be randomized within each OSN setting.
- The OSN Auto condition will be presented either at Visit 1 or at Visit 2 – in between the two other settings (see Figure 1).
- The training for Visit 1 is performed in a fixed order: first +4 dB SNR with OSN OFF (relatively easy condition and condition used for screening), then -4 dB SNR with OSN ON (relatively more difficult condition).

VISIT 3

- At the third visit, 4 lists will be tested in total (including training) for a total testing time of 32 minutes. About 45 minutes should be taken into account to conduct pupillometry at the third visit (including breaks).

All subjects will perform Visit 3 as follows:

Visit 3 (all ID no.)										
	OSN Auto					OSN OFF				
SNRs	-8	-4	0	4	8	-8	-4	0	4	8
Training (fixed order)				X					X	
Test (Randomized order)				X					X	

Additionally, the following applies:

- The training is performed in a fixed order: first +4 dB SNR with OSN Auto (relatively easy condition), then +4 dB SNR with OSN OFF (relatively more difficult condition).
- The first OSN setting (Auto or OFF) will be balanced between subjects (50% of the subjects will start with OSN Auto and 50% of the subjects will start with OSN OFF).

Amendment 1

Date: 21/01/2020
Non-substantial amendment to CIP BC103 (version 2, dated 09/09/2019)
Principal Investigator: William Brassington
Study Site Name: Queen Elizabeth, University Hospitals Birmingham NHS Foundation Trust, B15 2TH

See below the original text and the amended text. The amended text is in red.

Text in CIP version 2 dated 09/09/2019 (page 19, Sec. 8.3.1):

[...]. An eye tracking camera will be placed in front of the test person approximately 60 cm from the eyes.

is replaced with the amended sentence:

[...]. An eye tracking camera will be placed in front of the test person approximately in a range of 6 cm from the eyes.

Signature of Chief Investigator: ...

Date: .....24/1/2020.....

Signature of sponsor's representative: .....

Marcus Holmes
Snr Director, Clinical Affairs

Date: 2020-01-27