Study title: **Evaluation of clinical performance of Ponto implantation using a minimally invasive surgical technique – a prospective multicentre study**

NCT number: NCT04606823

**Revision history:**

| *Revision no* | *Date* | *Description* |
|---|---|---|
| 0 | 28-May-2020 | First version |
| 1 | 28-May-2020 | Re-routed without changes to align revision no. (internal) and version no. (external) |
| 2 | 26-Jun-2020 | Small change in indication for use for the MONO surgery kit.<br>Addition of pain- and numbness assessment at screening. |

CONFIDENTIAL

| | |
|---|---|
| **Clinical Investigation Title** | Evaluation of clinical performance of Ponto implantation using a minimally invasive surgical technique – a prospective multicentre study |
| **Investigation Code** | BC108 |
| **Investigational Device** | MONO Surgery kit |
| **Coordinating/Principal Investigators** | 1. Guy's and St Thomas' Hospitals, London, UK<br>*Dr Harry Powell*<br>2. Addenbroke's Hospital, Cambridge, UK<br>*Dr James Tysome*<br>3. Queen Elizabeth Hospital, Birmingham, UK<br>*Dr Rupan Banga*<br>4. Sahlgrenska University Hospital, Gothenburg, Sweden<br>*Dr Måns Eeg-Olofsson*<br>5. Aalborg University Hospital, Aalborg, Denmark<br>*Dr Dan Dupont Hougaard*<br>6. Odense University Hospital, Odense, Denmark<br>*Dr Jens Højberg Wanscher*<br>7. Radboud University Medical Center, Nijmegen, The Netherlands<br>*Dr Myrthe Hol* |
| **Sponsor** | Oticon Medical AB<br>Datavägen 37B<br>436 32 Askim<br>Sweden |

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## STATEMENT OF COMPLIANCE

This clinical investigation will be performed in consistency with the current version of the Declaration of Helsinki, ISO 14155, the Medical Device Directive (MDD) 93/42/EEC, Regulation (EU) 2017/745 (MDR) and applicable regional or national regulatory requirements as well as any additional requirements imposed by the Ethical Committee's.

# 1 SYNOPSIS

| | |
|---|---|
| **Clinical Investigation Title** | Evaluation of clinical performance of Ponto implantation using a minimally invasive surgical technique – a prospective multicentre study |
| **Investigation Code** | BC108 |
| **Investigational Device** | MONO Surgery kit |
| **Coordinating investigator** | 1. Dr Harry Powell<br>Consultant ENT Surgeon<br>St Thomas' Hearing Implant Centre, Guy's and St Thomas' NHS Foundation Trust<br>Westminster Bridge Road, London SE1 7EH, England |
| **Principal investigator(s):** | 2. Dr James Tysome<br>Consultant ENT and Skull Base Surgeon<br>ENT Department, Cambridge University Hospitals NHS Foundation Trust<br>Cambridge Biomedical Campus, Hills Road, Cambridge CB2 0QQ, England<br>3. Dr Rupan Banga<br>Consultant ENT Surgeon<br>ENT Department, Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham NHS Foundation Trust<br>Mindelsohn Way, Edgbaston, Birmingham, B15 2WB, England<br>4. Dr Måns Eeg Olofsson<br>ENT Surgeon<br>ENT Department, Sahlgrenska University Hospital<br>Gröna Stråket 11, 413 46, Gothenburg, Sweden<br>5. Dr Dan Dupont Hougaard<br>ENT Surgeon<br>Department of Otolaryngology, Head & Neck Surgery & Audiology, Aalborg University Hospital<br>Hobrovej 18-22, 9000 Aalborg, Denmark<br>6. Dr Jens Højberg Wanscher<br>ENT Surgeon<br>ENT Department, Odense University Hospital<br>J. B. Winsløws Vej 4, indgang 23, 5000 Odense, Denmark<br>7. Dr Myrthe Hol<br>ENT Surgeon<br>Department of Otorhinolaryngology, Hearing & Implants, Radboud University Medical Center<br>Route no. 377, Philips van Leydenlaan 15, 6525EX, Nijmegen, The Netherlands |
| **Sponsor:** | Oticon Medical AB<br>Datavägen 37B<br>436 32 Askim<br>Sweden |

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| **Objectives:** | The overall objective of this study is to prospectively study the rate of successful BAHS use after implantation of a Ponto implant using the MONO surgical procedure.<br>Primary Objective:<br>• Investigate the proportion of Ponto implant/abutment complexes providing a reliable anchorage for a sound processor three months after MONO surgical procedure<br>Secondary Objectives:<br>• Investigate the proportion of Ponto implant/abutment complexes providing a reliable anchorage for a sound processor<br>• Investigate the rate of implant survival<br>• Investigate the rate of implants perceived as stable<br>• Assess the skin condition around the abutment<br>• Investigate post-operative events around the abutment<br>• Investigate patient-perceived pain around the abutment<br>• Investigate patient-perceived numbness around the abutment<br>• Evaluate duration of surgery<br>• Investigate average implant (SP) usage by patients<br>• Investigate patient-reported benefit after surgery |
| **Safety objective:** | To investigate the occurrence and severity of adverse events related to the investigational device and associated procedures. All adverse events will be registered and listed. |
| **Methodology:** | A 12 months prospective, multinational, multicentre, single-arm investigation designed to follow clinical practice for bone conduction devices |
| **Products:** | Use of MONO Surgery kit and related accessories for the installation of Ponto implants (4 mm) with abutment lengths 6, 9, 12 and 14 mm; all developed by Oticon Medical AB (Gothenburg, Sweden). |

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| **Inclusion/exclusion criteria:** | Inclusion criteria:<br>• 18 years of age or older<br>• Patient indicated for surgical intervention with a bone anchored hearing system<br>• Signed informed consent<br>• Adequate bone quality to allow for a Ponto implant insertion, as judged by the investigator, and an expected bone thickness above 5 mm, where no complications during surgery are expected.<br>• Skin thickness of 12 mm or less at the implant site<br>Exclusion criteria:<br>• Patient undergoing re-implantation<br>• Patient who are unable or unwilling to follow investigational procedures/requirements, e.g. to complete quality of life scales<br>• Known condition or previous treatment that could jeopardize skin condition and wound healing over time as judged by the investigator (e.g. uncontrolled diabetes, previous radiotherapy in the area of interest)<br>• Known medical condition that contraindicate surgery as judged by the investigator<br>• Known and/or planned pregnancy at time of surgery<br>• Any other known condition that the investigator determines could interfere with compliance or investigation assessments<br>• Simultaneous participation in another clinical investigation with pharmaceutical and/or medical device which might cause interference with investigation participation |

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| **Endpoints:** | <u>Primary Endpoint:</u><br>The primary endpoint, 'capability of implant/abutment complex to provide a reliable anchorage for the sound processor three months after MONO surgical procedure', is a composite endpoint consisting of five separate endpoints that all need to be fulfilled;<br>I. Implant/abutment complex in situ<br>II. Implant stability<br>III. Absence of:<br>a. Holgers score ≥ 2, preventing use of sound processor<br>b. Patient-reported pain preventing use of sound processor<br>c. Skin overgrowth preventing use of sound processor<br><br><u>Secondary Endpoints:</u><br>Secondary endpoints are assessed at 9 days, 5 weeks, 3-, 6- and 12 months post-surgery if not otherwise stated.<br>• Capability of implant/abutment complex to provide a reliable anchorage for the sound processor after MONO surgical procedure at 6- and 12 months<br>• Implant in situ<br>• Implant stability (clinical)<br>• Holgers score (scale 0–4)<br>• Holgers score across visits during 0–3 months and 0–12 months post-surgery<br>• Max Holgers score per patient during 0–3 months and 0–12 months post-surgery<br>• Mild/Adverse skin reaction per patient during 0–3 months and 0–12 months post-surgery (adverse skin reaction defined as Holgers ≥ 2 on at least one follow-up visit)<br>• Total and individual IPS scores (scale I: 0–4; P:0–2; S: 0–2)<br>• Wound healing<br>• Skin dehiscence<br>• Skin overgrowth<br>• Patient-perceived pain (scale 0–10)<br>• Patient-perceived numbness (scale 0–10)<br>• Length of surgery<br>• Average sound processor usage time at 3, 6 and 12 months<br>• GBI benefit scores at 3 months |
| **Number of subjects:** | 50 |
| **Duration of study period:** | 12 months |
| **Statistical methods:** | Descriptive statistics will be used. The distribution of categorical and dichotomous variables will be given as number and percentage. In addition, the primary endpoint variable will also be presented by point estimates of the proportions combined with a two-sided 95% CI. The distribution of continuous variables will be given as Mean, standard deviation, Median, Minimum and Maximum. |
| **Investigation plan prepared by:** | Sara Svensson, Oticon Medical AB |

# 2 TABLE OF CONTENTS

# 3 LIST OF ABBREVIATIONS

| | |
|---|---|
| *ADE* | *Adverse Device Effect* |
| *AE* | *Adverse Event* |
| *BAHS* | *Bone Anchored Hearing System* |
| *CA* | *Competent Authority* |
| *CI* | *Confidence Interval* |
| *CIP* | *Clinical Investigation Plan* |
| *CRF* | *Case Report Form* |
| *DD* | *Device Deficiency* |
| *EC* | *Ethics Committee (see also IRB)* |
| *eCRF* | *electronic Case Report Form (see also EDC)* |
| *EDC* | *Electronic Data Capture system (see also eCRF)* |
| *ENT* | *Ear-, Nose and Throat* |
| *GBI* | *Glasgow Benefit Inventory* |
| *GCP* | *Good Clinical Practice* |
| *GDPR* | *General Data Protection Regulation (EU)* |
| *ISF* | *Investigator Site File* |
| *IPS* | *Inflammation, Pain, and Skin height* |
| *IRB* | *Institutional Review Board (see also EC)* |
| *ISO* | *International Organization for Standardization* |
| *MIPS* | *Minimally Invasive Ponto Surgery* |
| *OM* | *Oticon Medical* |
| *NRS* | *Numerical Rating Scale* |
| *PI* | *Principal Investigator* |
| *SADE* | *Serious Adverse Device Effect* |
| *SAE* | *Serious Adverse Event* |
| *SAP* | *Statistical Analysis Plan* |
| *SD* | *Standard Deviation* |
| *SSD* | *Single Sided Deafness* |
| *TMF* | *Trial Master File* |
| *TP* | *Tissue Preservation* |
| *USADE* | *Unanticipated Serious Adverse Device Effect* |

# 4 INTRODUCTION

Percutaneous bone anchored hearing systems (BAHS) were introduced in 1977 [1] and have now been used clinically for over 30 years. The BAHS technique utilises the body's natural ability to transfer sound in bone; a phenomenon known as bone conduction. By installation of an implant/abutment complex that is coupled to a sound processor, sound can be picked up and converted into vibrations that are transferred through the skull bone to the inner ear(s) (cochlea). Thus, sound can be transmitted directly to the cochlea and bypass any problems in the ear canal or middle ear. Today, more than 200,000 implantations have been made around the world. The long-term success rate of BAHS surgery is high, with a low rate of major complications [2].

## 4.1 The Ponto system

The Ponto system is a percutaneous bone conduction hearing system intended for improvement of hearing for patients with conductive and mixed hearing losses by unilateral or bilateral fitting, and for patients with Single Sided Deafness (SSD). The systems work independently of the outer and middle ear and utilizes the established direct drive bone conduction principle [3] to transmit vibrations (sound) from an external sound processor, via an implant in the temporal bone, to the inner ear.

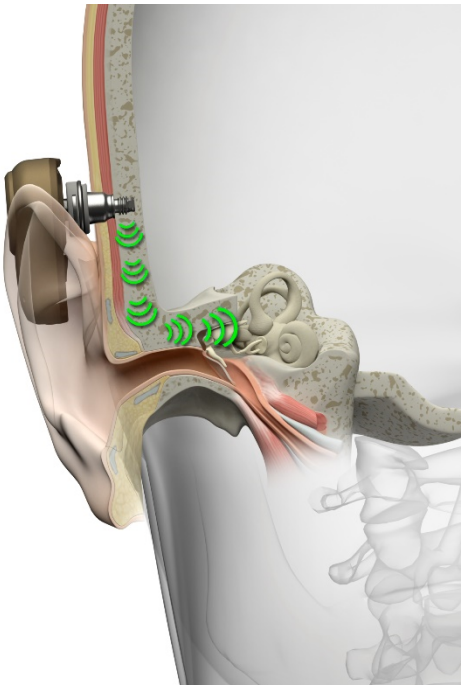

Figure 1. Percutaneous bone conduction device

The sound is picked up by the microphone and converted to vibrations in the sound processor. The sound processor is mechanically attached to an abutment mounted on a titanium screw implanted in the temporal bone. The vibrations are transferred to the skull via the implanted screw and the signal conveyed by the skull is picked up by the cochlea. The vibrations are transferred directly to the skull without skin attenuation.

To achieve the intended benefit of the Ponto system the abutment/implant complex must be firmly attached to the bone. There are different surgical methods used for the implantation; all using the three steps outlined below.

- Penetration of the skin and gaining access to the bony surface of the skull
- Drilling a seat for the implant
- Inserting the implant

## 4.2 Surgery developments

For many years, the BAHS surgical procedures involved extensive removal of the soft tissue surrounding the percutaneous abutment, so called tissue reduction. The aim of this traditional surgical procedure was to achieve a thin hairless skin that was well fixated to the underlying periosteum to hinder skin movement around the abutment and to facilitate cleaning. Over time, a variety of surgical modifications of the tissue reduction approach have been described and implemented in clinical practice, of which the (less invasive) linear incision technique was superior in terms of complication rates [2, 4]. Although the tissue reduction techniques worked very well for

the majority of patients, drawbacks such as large amount of scar tissue formation and numbness in the area around the abutment, skin thickening, and a less attractive cosmetic appearance with a bald spot were often encountered [5].

Around 10 years ago, BAHS surgical procedures without soft tissue reduction were reported. The linear incision with tissue preservation technique was first described by Hultcrantz in 2011 [5], and resulted in less scarring, good sensibility around the abutment and better cosmetics when compared to previous surgical procedures with skin thinning. The healing was also faster due to less surgical trauma and the length of the surgery was reduced. Along with the development of longer abutments, tissue-preserving surgical techniques soon became the new golden standard for BAHS implantations because of its favourable post-operative outcomes [6-8]. However, surgical developments continued in order to simplify and optimize the procedure further to improve surgical outcomes. In 2014, the Minimal Invasive Ponto Surgery (MIPS) was introduced. It was based on the previously described punch only-concept [9, 10], in which the surgery was performed and the device implanted trough a punched hole without any need to further incise the skin. The MIPS-kit included surgical instrumentation to ensure sufficient irrigation of the bony tissues while drilling, to protect the surrounding soft tissues and to ensure a correct drilling depth to maintain the safety of the procedure. MIPS has obtained increasing popularity and is used among surgeons worldwide. The use of MIPS has reduced the surgery time even more, improved cosmetic outcomes and decreased numbness in the area around the abutment to a minimum [11, 12].

Following the introduction of MIPS, the so-called MONO technique has been developed to further improve and simplify the surgical technique. In the MONO surgical procedure, the osteotomy is created using one drilling step in contrast to the three-step drilling procedure used so far. Further, MONO drills are of a novel parabolic design whereas MIPS utilises regular twist drills and the conventional techniques use round burrs and countersink. The parabolic design offers more effective bone dust removal compared with other drill designs, and tests have shown that the MONO drill generates minimal heat when used according to instructions. By using a one-step drilling procedure, the need for drill hole alignment is eliminated. Furthermore, less discomfort for the patient is expected since the drilling procedure is performed in one step instead of three.

The vast majority of adult patients are implanted with 4 mm implants as seen both in sales numbers and clinical study activities. Already today, some BAHS clinics have modified the surgical procedure in adults to include only two drill steps (i.e. off-label use), thus drilling directly for a 4 mm implant. The MONO drill together with the Cannula has a drill depth of 4.75 mm, which is 0.15–0.2 mm less deep than the surgical techniques used today (i.e. MIPS and the linear incision technique) when drilling for a 4 mm implant. For MIPS, the corresponding drill depth is 4.9 mm when used with the Cannula (3.9 mm for 3 mm implants), whereas the conventional round burrs have a drill depth of 5.0 mm (4.0 mm when drilling for 3 mm implants). Retrospective studies using computed tomography scans to analyse skull bone thickness in the area for BAHS placement show the average thickness to be 6.78 ± 2.06 mm (with chronic ear disease, n=65) and 6.90 ± 2.27 mm (without chronic ear disease, n=95) in adults in the U.S. [13], whereas a study in South Korea showed an average bone thickness between 6.17 and 7.41 mm for patients aged 10 years and above (divided into eight age groups with 10-year intervals, n=20 per group) [14]. A plot of individual bone thickness measurements indicates that 95% of the adult South Korean population has bone thickness of 5 mm or above [14].

This prospective study will investigate the clinical outcomes after using the MONO surgical procedure.

# 5 IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATIONAL DEVICE

## 5.1 Investigational Device description

The MONO Surgery kit includes single-use, pre-sterile instruments and tools used in bone anchored hearing implant surgery. The MONO Surgical kit comprises a Cannula, a MONO drill, an Insertion indicator and a Soft healing cap (Figure 2), with specifications according to Table 1.

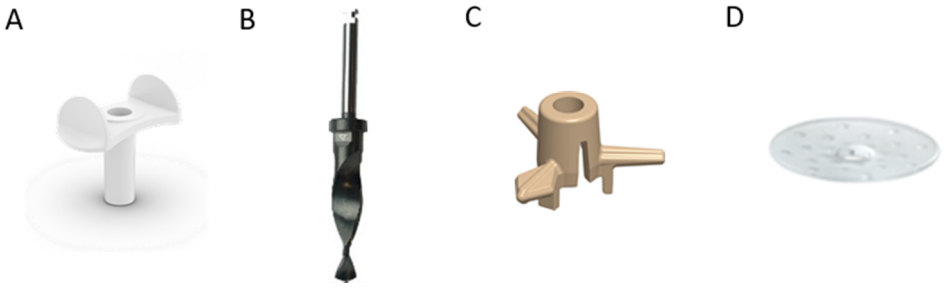


Figure 2. Products included in the MONO Surgery kit: Cannula (A), MONO drill (B), Insertion indicator (C) and Soft healing cap (D).

Table 1. Mono surgical kit specifications

| **Component** | **Characteristic** | **Specification** |
|---|---|---|
| Cannula | Dimensions (overall) | 25 x 14 x 24.6 mm |
| | Height (skin thickness) | 14 mm |
| MONO drill | Total length | 43.25 mm |
| | Drill depth | 4.75 mm |
| | Drill diameter | 3.8 mm (osteotomy) 4.8 mm (flutes) |
| | Hub/stop diameter | 6.0 mm |
| | Maximum drill speed | 2000 rpm |
| | Drill hand piece | 20:1 spindle speed ratio |
| | Drill connection | ISO 1797:2017 Dentistry — Shanks for rotary and oscillating instruments |
| Insertion indicator | Dimensions | Ø 22 mm<br>H 11.35 mm |
| Soft healing cap | Dimensions | Ø 26 mm |

All materials in the kit components that come, or may come, in direct contact with the patient are biocompatible. The materials and their estimated human tissue exposure time are outlined in Table 2. The Cannula and the MONO drill are in direct contact with the patient's soft tissue and bone for limited period of time (minutes/seconds). The Insertion indicator is normally not in contact with the patient but may come in contact with the skin for a few seconds. The Soft healing cap is positioned above the skin surface and dressing is applied between the soft healing cap and the skin. It is normally not in direct contact with the human body but may come in contact with the patient's skin during connection/disconnection. The soft healing cap may be used for extended periods and may then be in contact with the patient's skin.

Table 2. Mono Surgery kit materials

| **Component** | **Material** | **Classification of body contact** |
|---|---|---|
| Cannula | PBT (Polybutylene terephthalate) | Tissue/bone – limited exposure |
| MONO drill | Stainless steel with partial DLC coating | Tissue/bone – limited exposure |
| Insertion indicator | PEEK (Poly-ether-ether ketone) | Skin – limited exposure (abnormal use) |
| Soft healing cap | Thermoplastic elastomer (TPE) | Skin – prolonged exposure |

#### *5.1.1 Intended use*

The MONO Surgery kit is an accessory to the Ponto implant system, a part of the Ponto hearing system.

*Intended use Ponto implant and Ponto system*

The Ponto bone anchored hearing system's intended use is for improvement of hearing for patients with conductive or mixed hearing losses, whether unilaterally or bilaterally fitted, or for those with single-sided deafness.

The intended use of the Ponto Implant is surgical placement into the temporal bone to act as permanent anchorage as means to attach the sound processor.

*Intended use of MONO Surgery kit*

The **MONO Surgery kit** is intended for use in surgery for a bone anchored hearing implant.

- The **MONO drill** is intended for use to create the osteotomy in the skull bone in a one-step drilling procedure. The MONO drill is used together with the **Cannula**, which protects the soft tissue during drilling and ensures correct drill depth by providing a hard stop with the drill.
- The **Insertion indicator** is intended for use during implant insertion as a guide to visualise correct placement/insertion of the implant.
- The **Soft healing cap** is intended to be attached to the abutment during the soft tissue healing period after bone anchored implant surgery to hold the dressing in place and act as protective mechanical barrier.

### 5.2 Manufacturer

The Mono Surgery kit is manufactured by Oticon Medical AB, Askim, Sweden. Oticon Medical AB is ISO 13485 certified and has CE marked and FDA-cleared products for hearing healthcare on the market.

### 5.3 Identification of the Investigational Device

Full identification details of the MONO Surgery kit are listed in Table 3.

Table 3. Identification details of investigational device

| Name | Article number | Description |
|---|---|---|
| **MONO Surgery kit** | 220701 | *The MONO Surgery Kit, is used in the MONO single-stage procedure for installation of 4 mm Ponto Implants with the wide 4.5 mm diameter design. The kit consists of Cannula, MONO drill, Insertion indicator and Soft healing cap.* |

### 5.4 Traceability

The Mono Surgery kits are traceable by a lot number. All kits used in this clinical investigation will have the same lot number.

## 5.5 Population and indications

### *5.5.1 Indication for use Ponto implant and Ponto system*

The Ponto system is intended for the following patients and indications:

- Patients with conductive or mixed hearing losses, who can still benefit from amplification of the sound. The pure tone average (PTA) bone conduction (BC) threshold (measured at 0.5, 1, 2 and 3 kHz) of the indicated ear should be better than or equal to 45 dB HL for use with the Ponto Plus, Ponto 3 and Ponto 4 sound processors, 55 dB HL for use with the Ponto Pro Power, Ponto Plus Power and Ponto 3 Power sound processors and 65 dB HL for use with the Ponto 3 SuperPower and Ponto 5 65 sound processors.
- Bilateral fitting is applicable for most patients having a symmetrically conductive or mixed hearing loss. The difference between the left and right sides' BC thresholds should be less than 10 dB on average measured at 0.5, 1, 2 and 4 kHz, or less than 15 dB at individual frequencies.
- Patients who have a profound sensorineural hearing loss in one ear and normal hearing in the opposite ear (i.e. single sided deafness or "SSD"). The pure tone average (PTA) air conduction (AC) threshold of the hearing ear should then be better than or equal to 20 dB HL (measured at 0.5, 1, 2 and 3 kHz).
- Also indicated for any patient who is indicated for an air-conduction contralateral routing of signals (AC CROS) hearing aid, but who for some reason cannot or will not use an AC CROS.

### *5.5.2 Indication for use MONO Surgery kit*

Within the Ponto BAHS indicated patient population, the use of MONO surgical technique for Ponto BAHS implant installation is indicated for:

- Adult patients with normal anatomy and expected bone thickness of at least 5 mm, where no complications during surgery are expected.
- Patients, as per above, with a skin thickness of 12 mm or less.

Use of MONO surgical technique is contraindicated for children and patients with expected bone thickness below 5 mm.

## 5.6 Training and Experience

The MONO Surgery kit will be used by ear, nose and throat (ENT) surgeons experienced with bone conduction systems.

In this clinical investigation, all surgeons have previous experience with the existing Minimal Invasive Ponto Surgery (MIPS) surgical technique, that similar to MONO surgery performs the implant site preparation through the Cannula. Prior to initiation of the investigation, the surgeons will be trained in all procedures related to handling and use the MONO Surgery kit. In addition, clinical support representatives from the sponsor may be present during surgery to provide advice and support. Patients will be informed and consent to the presence of sponsor representatives during surgery.

## 5.7 Surgical procedure

A circular incision is made using a standard 4–5 mm biopsy punch. The Cannula is placed in the incision to establish a port of entry through the soft tissue. The MONO drill is inserted through the Cannula and used to create the desired osteotomy for a 4 mm Ponto implant (Ø 4.5 mm), in one step.

During implant installation, the Insertion indicator is used as a guide to visualize correct placement/insertion turns of the implant.

Following implant installation, the Soft Healing Cap is attached to the abutment to hold the dressing in place and act as protective mechanical barrier during the soft tissue healing period after bone anchored implant surgery.

Surgical details are to be found in the Surgical Manual and the Addendum to Surgical Manual (MONO surgical procedure).

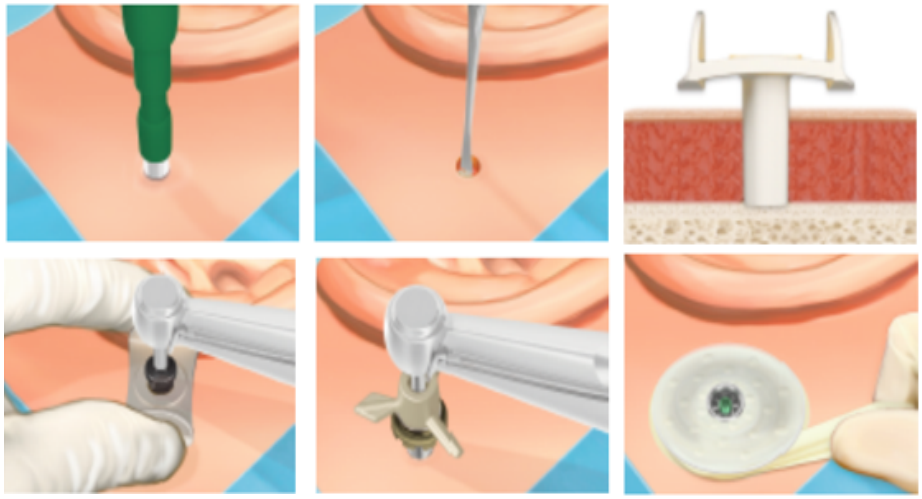

Figure 3. Stepwise illustration of the MONO surgical procedure.

## 6 JUSTIFICATION FOR THE INVESTIGATION

The investigation is a multinational, multicentre, prospective, single-arm investigation on the MONO Surgery kit. The purpose of this investigation is to establish the level of successful implant/abutment complex installations using the MONO surgical procedure.

The justification of the clinical investigation is based on the clinical evaluation, which includes an assessment and analysis of clinical data concerning safety and performance of the investigational device and similar devices.

### 6.1 Summary of comparable devices/treatment options (state-of-the-art)

The MONO Surgery kit that will be investigated in this study is an accessory to a percutaneous implant. The surgical procedure for the placement of percutaneous BAHS implants has been evolving since the launch and CE marking of the Ponto system in June 2008. The initial method involved extensive removal of subcutaneous soft tissue (known as tissue reduction surgery) in the area of implantation, and since then the surgical technique has become less and less invasive. Today the prevailing surgical methods are the so-called linear incision with tissue preservation and punch only/MIPS (Minimal Invasive Ponto Surgery).

The intended use of the MONO Surgery kit is fulfilled when the implantation results in a percutaneous implant/abutment complex that is capable of holding the sound processor in place. The fulfilment of the MONO Surgery kit intended use (and its indirect patient benefit) is therefore not possible to verify in vivo without a connection to the outcomes of the implantation.

In a recent systematic review [15], the literature reporting on the Ponto bone anchored hearing system was reviewed. In total, data from 1,352 patients were included in the review.

Audiological outcomes were discussed in 20 publications. Improvement against the unaided

thresholds was demonstrated. The functional improvement was on average 33.9 dB. The effective gain, or remaining air-bone-gap was on average 6.7 dB. All evaluated data showed aided speech reception thresholds significantly below normal speech level. Five studies reported quality of life using the Glasgow Benefit Inventory, 98% reported an improvement when analysing the score on an individual level.

The data on the implant system confirmed earlier findings and refined the knowledge on complication rates. Major complications (intra- or postoperatively) are very rare, with no life-threatening complications reported in the summarized data. The overall implant survival rate was 98%, with an average follow-up time of 17 months (0.25-60 months). Skin reactions are the most common complication. A Holgers score ≥ 2 generally warrants treatment; typically local treatment for a Holgers score of 2, with the addition of systemic antibiotic treatment for a Holgers score of 3. Across the studies included in the review, reactions classified as Holgers 2 or higher occurred in 5% of visits and 15% of patients.

### 6.2 Justification of the investigation design and outcome measures

The investigation has a single-arm design, reflecting the typical study design in the field. The investigational device is used within its intended purpose and for patients within its indicated use. The investigation sites are renowned clinics with ENT specialists experienced in BAHS implantations and follow-up, ensuring professional patient recruitment and care. The visiting schedule follow the standard practice at the respective clinics and includes 1–3 extra visits compared to patients treated outside of the investigation, enabling close follow-up on performance and safety.

The primary endpoint of the investigation is the capability of the implant/abutment complex to provide a reliable anchorage for the sound processor three months after the MONO surgical procedure. It is comprised of five variables related to the performance and functionality of the implant/abutment complex. All variables included in this composite endpoint are commonly assessed in clinical investigations, underscoring its scientific relevance.

The safety objective is to investigate the occurrence and seriousness of adverse events (AE) related to the investigational device and corresponding procedures. The safety endpoint comprises adverse events, occurring both intra- and post-operatively.

The primary endpoint is set at three months, which is considered as a relevant time period for evaluation of the outcomes after a surgical procedure. Once osseointegration of the implant has been achieved, and the primary healing of the surgical wound has occurred, the surgical technique used is not deemed to influence the capability of the implant to provide a reliable anchorage for the sound processor. It is therefore sufficient to evaluate only short-term data. Data will also be compiled after a 12-months period, to confirm longer-term safety and performance of the devices.

The results of the investigation will be important for the understanding of outcomes related to the BAHS treatment in general and for the MONO surgical procedure and the subsequent performance of the implant/abutment complex in particular.

## 7 RISKS AND BENEFITS OF THE INVESTIGATIONAL DEVICE AND CLINICAL INVESTIGATION

The investigational device used in the study is the MONO Surgery kit. The device is CE marked and used within its intended use. Minimal risks are expected for subjects participating in the current study.

Treatment and rehabilitation will not differ significantly for participating research subjects

compared to patients undergoing a BAHS procedure outside the study. The implants and abutments are CE-marked, thus identical to the ones used in a regular surgery. The surgical technique used in the study (MONO technique) is a further development of the MIPS technique. It is a simplified technique utilizing one drilling step in contrast to the three-step drilling procedure used today. The drill depth with the MONO drill together with the Cannula is 4.75 mm, which is 0.15–0.2 mm less deep than the surgical techniques used today when drilling for a 4 mm implant – the far most common implant used for adults. By using a one-step drilling procedure, the need for drill hole alignment is eliminated. Tests have also shown minimal heat generation during drilling when used according to instructions. Furthermore, less discomfort for the patient is expected since the drilling procedure is performed in one step rather than three.

Post-operative procedures are the same for participating research subjects compared to patients undergoing a BAHS procedure outside the study, thus not contributing to any additional risk. The only exceptions from the routine procedure are the use of a patient questionnaire (see section 10.3.9), which will extend the duration of one of the visits, and one to three additional visit(s) after surgery (vary between investigation sites).

Per above, participation in the study will result in a higher frequency and duration of follow-up visits. This will require an extra effort for the subject. On the other hand, the subject will have the opportunity to interact more with the treating physician and other relevant personnel, which by some may be considered as advantageous. Treatment of possible complications for study subjects will be the same as for regular implant patients. All adverse events will be registered and taken into consideration when compiling the final report. For information about anticipated adverse device effects (ADEs), see section Complications in the Surgical Manual.

Subjects enrolled may not personally benefit from participating in this study, but the knowledge and experiences gathered may lead to development of safer and more efficient BAHS products and surgical procedures for others.

## 7.1 Residual risks and Anticipated adverse device effects

Risk management process to identify and manage risks according to ISO 14971:2019 has been implemented covering the whole life cycle of the MONO Surgery kit. Qualitative and quantitative aspects of clinical safety of risks have been examined and documented as part of the process. The identified risks have been mitigated as far as possible and all residual risks are anticipated to be acceptable (according to the Sponsor's risk acceptability criteria). Anticipated adverse device effects as a result of the residual risks are summarized below.

### *7.1.1 Risks associated with use of the Ponto system*

Patients who meet the indications for implantation should be informed about typical risks associated with surgery (effects from general anesthesia, infections, etc.), which are independent of the product itself. This also includes temporary numbness and/or pain that could occur during the healing period.

Serious complications during surgery (e.g. heavy bleeding (not controlled using standard hospital practice), epidural hematoma, intracranial injury) are rare, but should be carefully considered. No reports of the mentioned complications have so far been identified through the company's Post Market Surveillance.

Explantation may be required e.g. in the following cases: device failure (e.g. caused by head trauma), medical or surgical complication (persistent skin infection), need of radiation therapy, or

deterioration of hearing (outside of indicated use). Often, but not always, the abutment alone can be removed, leaving the implant in position under the skin; this is in most cases a minor procedure and requires no additional surgery.

Harm associated with the implant surgery (such as persistent numbness and/or pain) and use, (such as skin overgrowth) are accounted for in the risk analysis. These risks have been evaluated, and the materials and design of the implant have been chosen to minimize these risks.

Minor infections may occur in the area of the percutaneous abutment during use and are often handled by local treatment (hygienic recommendations to avoid local infections are made in the Surgical Manual).

The use of the sound processor carries low risks (typically temporary discomfort or that the patient is unaided if e.g. the device malfunctions). Hazardous situations can however occur, e.g. if a battery is swallowed and leakage of the content occurs. These risks have been mitigated as far as possible by design of the sound processor.

In summary, the risks identified in the risk management process are typical for percutaneous implant systems. Similar systems have been on the market for several years without any reports of major complications. All identified risks have been reduced as far as possible and all residual risks are anticipated to be acceptable (according to the company's risk acceptability criteria) and outweighed by the medical benefits of the Ponto bone anchored hearing system.

#### *7.1.2 Risks associated with the MONO Surgery kit*

No new risks are anticipated with the MONO Surgery kit or the MONO surgical procedure, in addition to those identified above. However, probability of harm could differ.

All individual residual risks are anticipated to be acceptable (according to the company's risk acceptability criteria). No clinical data on the final design of the system under evaluation has been generated and the residual risk assessment is therefore based on state-of-the-art (including equivalent and bench-mark systems) as well as expert opinions.

### 7.2 Anticipated clinical benefits

#### *7.2.1 Expected benefits with the Ponto system*

Claims on clinical benefit:

- Improved ability to hear sounds
- Improved speech intelligibility
- Improved quality of life

#### *7.2.2 Expected benefits with the MONO Surgery kit*

The MONO Surgery kit is an accessory to the Ponto implant and part of the Ponto system and does not have a patient benefit in itself. However, a fully functional percutaneous "implant/abutment complex" is a prerequisite for the patient to have benefit of the Ponto system. Therefore, the indirect intended benefit of the MONO Surgery kit is here defined as that it provides a fully functional implant/abutment complex installation allowing loading and use of the sound processor (see section 10.3.1).

### 7.3 Risks associated with participation in the clinical investigation

The MONO Surgery kit will be used for implantation of Ponto implants by experienced ENT specialists with knowledge and training ensuring appropriate patient recruitment, effective patient

care and follow-up. All ENT specialists involved in the investigation are experienced in both the linear incision technique with tissue preservation and the MIPS technique, and will also receive training in the MONO surgical procedure and use of the MONO Surgery kit prior to initiation of the investigation.

The MONO Surgery kit is CE-marked and has been tested for reliability and biocompatibility to ensure the design of a reliable and safe product. Therefore, no additional risks other than those described in section 7.1 are expected due to participation in the investigation.

All participants in the investigation will attend frequent follow-up visits to monitor safety and performance of the Ponto implant/abutment complex installed by using the MONO surgical procedure. This will allow for the detection of any complications at an early stage and the possibility to take appropriate action. The subjects will have the opportunity to frequently interact with the treating physician and the assessments performed in the visits are non-invasive and closely follows clinical practice. All procedures, investigations and outcome measures in the clinical investigation are standard methods used in the field of BAHS research, and there are no assessments in the investigation that add additional risks to the patients.

### 7.4 Possible interactions with concomitant medical treatments

During surgery, no risks in relation to concomitant medication other than those associated with surgery in general (e.g. use of anticoagulants) are anticipated.

During the clinical investigation, medication which is considered necessary for the patient's safety and well-being may be given at the discretion of the investigator. The administration of this medication and all medication for adverse events must be recorded in the appropriate section of the electronic Case Report Form (eCRF).

### 7.5 Risk control and/or mitigation

The identified risks have been mitigated as far as possible through verified design considerations, process validation and information and warnings in instructions for use. All individual residual risks are acceptable (according to the manufacturer's risk acceptability criteria).

### 7.6 Risk-to-benefit rationale

Potential hazards associated with the implantation and use of the MONO Surgery kit have been through a comprehensive risk management process in accordance with ISO 14971. Overall, the residual risks associated with the use of the MONO Surgery kit are of low severity and comparable to similar products on the market when the system is used as intended.

Furthermore, this investigation has been designed to minimize the risks as far as possible. The inclusion of patients has been limited to only adults and the inclusion and exclusion criteria have been set to exclude patients with expected bone thickness less than 5 mm, or concomitant medical conditions that could increase the risk associated with investigation participation to unacceptable levels. No procedures or assessments in the investigation add additional risks to the patients. The investigation will be performed in accordance with applicable rules and regulations, and follow ethical and scientific standards for designing, conducting, recording and reporting clinical studies to ensure that the rights, safety and wellbeing of the participating patients are protected.

It is concluded that the benefits associated with implantation, e.g. by using the MONO Surgery kit, outweigh the overall residual risks. Furthermore, it is concluded that the anticipated risks associated with participation in the investigation are acceptable when weighted against the anticipated user benefits of participation.

# 8 OBJECTIVES AND ENDPOINTS

## 8.1 Primary objective

| Primary objective | Corresponding primary endpoint/outcome variable(s) | Section |
|---|---|---|
| A. To investigate the proportion of Ponto implant/abutment complexes providing a reliable anchorage for a sound processor three months after MONO surgical procedure | 1. Composite variable [Yes/No] including:<br>I. Implant/abutment complex in situ<br>II. Implant stability<br>III. Absence of:<br>a. Holgers score ≥ 2, preventing use of sound processor<br>b. Patient-reported pain preventing use of sound processor<br>c. Skin overgrowth preventing use of sound processor | 10.3.1 |

## 8.2 Secondary objective(s)

| Secondary objective(s) | Corresponding secondary endpoint/outcome variable(s) | Section |
|---|---|---|
| B. To investigate the proportion of Ponto implant/abutment complexes providing a reliable anchorage for a sound processor after MONO surgical procedure | 1. Composite variable [Yes/No] to be assessed at 6- and 12 months post-surgery including:<br>I. Implant/abutment complex in situ<br>II. Implant stability<br>III. Absence of:<br>a. Holgers score ≥ 2, preventing use of sound processor<br>b. Patient-reported pain preventing use of sound processor<br>c. Skin overgrowth preventing use of sound processor | 10.3.1 |
| C. To investigate the rate of implant survival | 1. Implant in situ [Yes/No] assessed at 9 days, 5 weeks, 3-, 6- and 12 months post-surgery | 10.3.2 |
| D. To investigate the rate of implant perceived as stable | 1. Implant stability [Yes/No] assessed at 9 days, 5 weeks, 3-, 6- and 12 months post-surgery | 10.3.3 |
| E. To assess the skin condition around the abutment | 1. Holgers score (scale 0–4) assigned by investigator at 9 days, 5 weeks, 3-, 6- and 12 months post-surgery<br>2. Max Holgers score per patient during 0–3 months and 0–12 months post-surgery<br>3. Mild/Adverse skin reaction per patient during 0–3 months and 0–12 months post-surgery (adverse skin reaction defined as Holgers ≥ 2 on at least one follow-up visit | 10.3.4.2 |

| | | | |
|---|---|---|---|
| | | including unplanned visits during the analysis period)<br>4. Total and individual IPS scores (scale I: 0–4; P: 0–2; S: 0–2) assigned by investigator at 9 days, 5 weeks, 3-, 6- and 12 months post-surgery<br>5. Wound healing [Yes/No] assessed at 9 days, 5 weeks, 3-, 6- and 12 months post-surgery<br>6. Dehiscence [Yes/No] measured at the widest point [millimetres] at 9 days, 5 weeks, 3-, 6- and 12 months post-surgery<br>7. Skin overgrowth [Yes/No] assessed at 9 days, 5 weeks, 3-, 6- and 12 months post-surgery | 10.3.4.3<br>10.3.4.1<br>10.3.5<br>10.3.4.3 |
| F. | To investigate post-operative events around the abutment | 1. Post-operative events assessed at 9 days, 5 weeks, 3-, 6- and 12 months post-surgery | 10.3.5 |
| G. | To investigate patient-perceived pain around the abutment | 1. Assessment of presence [Yes/No] and magnitude (scale 0–10) of patient-perceived pain at 9 days, 5 weeks, 3-, 6- and 12 months post-surgery | 10.3.6 |
| H. | To investigate patient-perceived numbness around the abutment | 1. Assessment of presence [Yes/No] and magnitude (scale 0–10) of patient-perceived numbness at 9 days, 5 weeks, 3-, 6- and 12 months post-surgery | 10.3.7 |
| I. | To evaluate duration of surgery | 1. Length of surgery [minutes] from punch to placement of healing cap | 10.2.1 |
| J. | To investigate sound processor usage by patients | 1. Average sound processor usage time [hours per day; days per week] at (5 weeks), 3, 6 and 12 months | 10.3.8 |
| K. | To investigate patient-reported benefit after surgery | 1. Glasgow Benefit Inventory (GBI) benefit scores as for total-, general-, social- and physical scores at 3 months | 10.3.9.1 |

## 8.3 Safety objective

| Safety objective | | Corresponding primary endpoint/outcome variable(s) | Section |
|---|---|---|---|
| L. | To investigate the occurrence and severity of adverse events related to the investigational device and associated procedures | 1. Number and severity of related adverse events reported from surgery throughout the investigation at 3- and 12 months<br>2. Number and severity of device deficiencies reported from surgery throughout the investigation at 3- and 12 months | 10.4<br>10.4 |

### 8.4 Risks and anticipated adverse device effects that are to be assessed

Anticipated device effects are summarized in section 7.1. In the investigation the principal investigator or designee is responsible for judging whether the appearance of any adverse event, including the events mentioned in section 7.1, are considered to be AEs or ADEs. Applicable events must be reported in the applicable section of the eCRF) according to the timelines and definitions mentioned in the AE section (section 19.3).

## 9 DESIGN OF THE CLINICAL INVESTIGATION

### 9.1 Investigation outline

This investigation is a 12-months prospective, multinational, multicentre, single-arm investigation on the performance and safety of the Ponto implant system implanted using the MONO surgical procedure. The primary aim of the study is to investigate the proportion of patients that are able to use their sound processor as intended three months after implantation, taking into consideration several different variables such as implant stability, skin reactions and pain. This composite endpoint is anticipated to be the most relevant outcome for the patient as it focuses on the usability of the device, which is the decisive factor for patient benefit. Additional outcomes investigated in the study include implant stability and survival, surgery length, subjective pain and numbness, skin conditions around the abutment, sound processor usage and patient benefit in terms of quality of life-questionnaire. In addition to primary endpoint data, long-term safety and performance will be evaluated over a 12-months period (Figure 4).

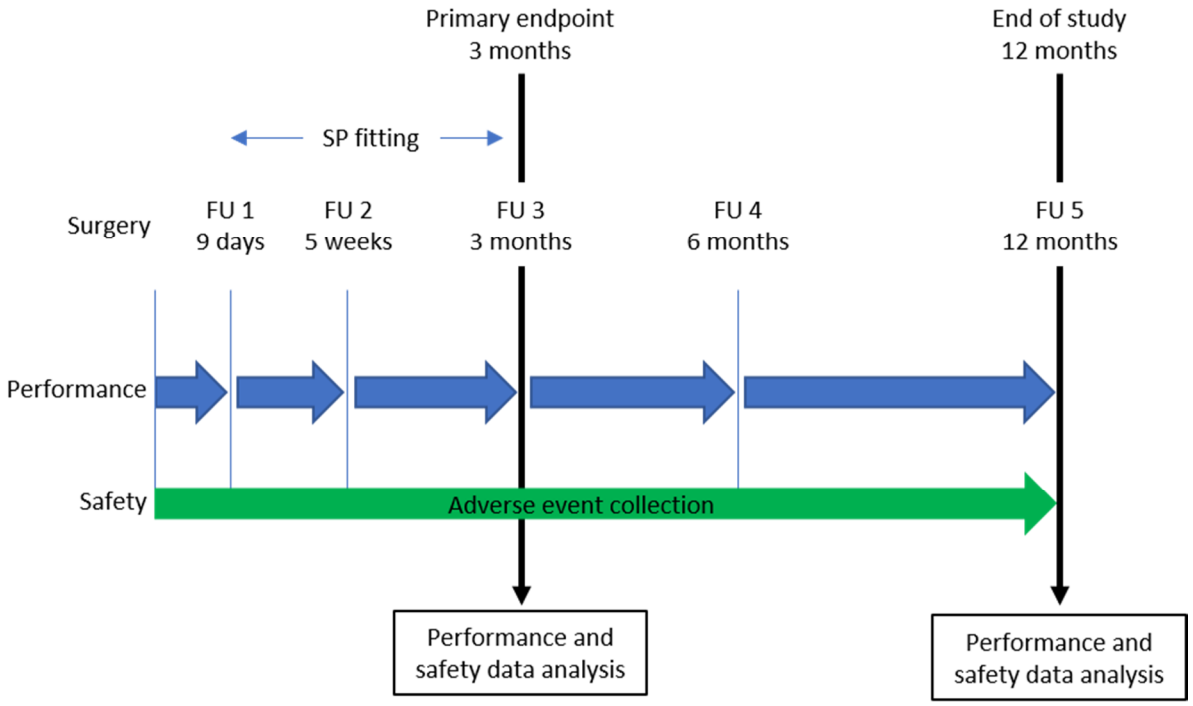


Figure 4. Overview of the clinical investigation

Patients considered for inclusion into this clinical investigation will be found among those who have already received audiological and otological evaluation and are found to be suitable candidates for BAHS treatment. Potential subjects will be asked by their ENT specialist to participate in the investigation, with the aim to include a total number of 50 subjects across all investigation sites. An informed consent form must be signed by the subject and investigator (or delegated site staff) before any procedures related to the investigation are performed and also before any information is recorded in the study-specific eCRFs.

Following screening and surgery, subjects will come for post-operative follow-up visits at 9 days*, 5 weeks*, 3 months, 6 months, and 12 months following implant installation. With some minor deviations, it is routine clinical practice for patients to visit the clinic at these intervals for follow-up. At each visit, a clinical evaluation of the surgical site and implant will be made, and a range of outcome measures related to implant, skin status and post-operative events are collected. Sound processor fitting/implant loading will be scheduled according to local clinical practice, which may vary across study sites and may fall outside the data collection visit intervals defined in this protocol. If the loading visit constitutes an additional follow-up not accounted for in the schedule, the study participant will be screened for adverse events and referred immediately for physical examination if necessary. At all visits, study participants will be screened for adverse events and referred immediately for physical examination if necessary.

*Will vary between the study sites, depending on their normal follow-up schedules.

All clinical and investigation-related data will be recorded in eCRFs. A schematic overview of the investigation visits and collected variables is shown in Table 4.

### 9.1.1 Clinical Investigation flow chart

Table 4. Flow chart of the investigation

| Protocol activity | V1 | V2 | V3 | V4 | V5 | V6 | V7 | Un-scheduled visit(s) |
|---|---|---|---|---|---|---|---|---|
| | Screening | Surgery | Surgical follow-up | Follow-up | Follow-up (Primary endpoint) | Follow-up | Follow-up (End of study) | |
| | Pre-surgery | 0 | 9 days | 5 weeks** | 3 months | 6 months | 12 months | N/A |
| | | | ± 3 days | ± 2 weeks | ± 1 week | ± 2 weeks | ± 1 month | N/A |
| Subject Eligibility | | | | | | | | |
| *Informed consent* | *X* | | | | | | | |
| *Inclusion/exclusion criteria* | *X* | *X* | | | | | | |
| *Baseline characteristics* | *X* | | | | | | | |
| *Medical and surgical history* | *X* | | | | | | | |
| Audiology | | | | | | | | |
| *Fitting Sound Processor** | | | ← | *X* | → | | | |
| Implantation | | | | | | | | |
| Surgical information | | *X* | | | | | | |
| Intra-operative events | | *X* | | | | | | |
| Post-operative assessment | | | | | | | | |
| Post-operative events | | | *X* | *X* | *X* | *X* | *X* | *X* |
| Skin assessments | | | *X* | *X* | *X* | *X* | *X* | *X* |
| Implant survival | | | *X* | *X* | *X* | *X* | *X* | *X* |
| Manual implant stability | | | *X* | *X* | *X* | *X* | *X* | *X* |
| Subjective pain and numbness assessment | *X* | | *X* | *X* | *X* | *X* | *X* | *X* |
| Sound processor usage | | | | *(X)* | *X* | *X* | *X* | |
| PRO's | | | | | | | | |
| GBI | | | | | *X* | | | |
| Safety | | | | | | | | |
| Adverse events assessment | | X | X | X | X | X | X | (X) |

** Sound processor fitting will occur according to local clinical practice, but no later than at the 3-month follow-up visit.*
*** The extended visit window is due to different local clinical practices regarding post-operative follow-up.*

## 9.2 Clinical investigation visits

When a subject has agreed to participate in the clinical investigation, the following assessments, measurements and/or actions will be performed, and corresponding data will be collected and recorded in the eCRF.

### 9.2.1 Visit 1: Screening

- Informed consent is obtained from the subject (see section 18)
- The subject is evaluated in respect to inclusion and exclusion criteria
- The subject's demographic data is collected and recorded

- Data concerning the patient's hearing impairment; medical history, and ongoing diseases and treatments, is recorded
- Pre-operative pain and numbness in the area of implant installation is assessed

#### *9.2.2 Visit 2: Surgery (and implant installation)*

- Surgical information recorded (see section 10.2)
- Medications given perioperatively recorded
- Intra-operative events (see section 10.2.3)

#### *9.2.3 Visit 3: Surgical follow-up*

- Removal of dressings and healing cap
- Implant survival (see section 10.3.2)
- Implant stability (see section 10.3.3)
- Skin condition assessments (see section 10.3.4)
- Pain assessment (see section 10.3.6)
- Numbness assessment (see section10.3.7)
- Assessment of post-operative events (see section 10.3.5)
- Safety assessment with collection of adverse events (see section 10.4)
- The patient is instructed on cleaning procedures

#### *9.2.4 Visit 4–7: Follow-ups*

- Implant survival
- Implant stability
- Skin condition assessments
- Pain assessment
- Numbness assessment
- Assessment of post-operative events
- Safety assessment with collection of adverse events
- Type of sound processor is recorded
- Average sound processor usage time is recorded (see section 10.3.8)
- Completion of GBI questionnaire (see section 10.3.9.1**Error! Reference source not found.**) (visit 5)

### 9.3 Investigational device

The investigational device is the MONO Surgery kit that is to be used in BAHS surgeries during temporal bone drilling, allowing for insertion of a Ponto implant. Further details on the investigational device can be found in section 5.1**Error! Reference source not found.**.

A new MONO Surgery kit is to be used for every surgery (single use), resulting in a total of at least 50 kits to be used in the study. (Extra kits will be provided to investigators to allow for bilateral surgeries.)

Other medical devices to be used in the investigation are listed in Table 5.

Table 5. Overview of devices to be used in the investigation and corresponding article numbers

| Name | Article number | Description |
|---|---|---|
| **Ponto BHX implant, 4 mm, with abutment, 6 mm** | 52168 | *The 4 mm Ponto BHX implant with pre-mounted 6 mm abutment is used in the single-stage surgical procedure and consists of implant, abutment and connection screw.* |
| **Ponto BHX implant, 4 mm, with abutment, 9 mm** | 52169 | *The 4 mm Ponto BHX implant with pre-mounted 9 mm abutment is used in the single-stage surgical procedure and consists of implant, abutment and connection screw.* |
| **Ponto BHX implant, 4 mm, with abutment, 12 mm** | 52170 | *The 4 mm Ponto BHX implant with pre-mounted 12 mm abutment is used in the single-stage surgical procedure and consists of implant, abutment and connection screw.* |
| **Ponto BHX implant, 4 mm, with abutment, 14 mm** | 52171 | *The 4 mm Ponto BHX implant with pre-mounted 14 mm abutment is used in the single-stage surgical procedure and consists of implant, abutment and connection screw.* |
| **Ponto wide implant, 4 mm, with abutment, 6 mm** | 51136 | *The 4 mm implant is used in the single-stage surgical procedure and consists of a pre-mounted 6 mm abutment, a connection screw and a 4 mm wide implant.* |
| **Ponto wide implant, 4 mm, with abutment, 9 mm** | 51137 | *The 4 mm implant is used in the single-stage surgical procedure and consists of a pre-mounted 9 mm abutment, a connection screw and a 4 mm wide implant.* |
| **Ponto wide implant, 4 mm, with abutment, 12 mm** | 51138 | *The 4 mm implant is used in the single-stage surgical procedure and consists of a pre-mounted 12 mm abutment, a connection screw and a 4 mm wide implant.* |
| **Ponto wide implant, 4 mm, with abutment, 14 mm** | 52065 | *The 4 mm implant is used in the single-stage surgical procedure and consists of a pre-mounted 14 mm abutment, a connection screw and a 4 mm wide implant.* |
| **Sound processor indicator** | 50428 | *The sound processor indicator is used on intact skin to illustrate the size of a sound processor in order to assess and enable marking of the appropriate implant site prior to incision.* |
| **Sterilisation cassette** | 52074 | *Sterilisation cassette holds instruments in place during sterilisation.* |
| **Counter torque wrench** | 51690 | *The counter torque wrench is used for counteracting the force when tightening or unscrewing the connection screw using the screwdriver. It is also used for manual tightening in the single-stage procedure if needed.* |
| **Torque wrench** | 50230 | *The Torque wrench, scale 10–35 Ncm, is used to secure the correct torque when tightening the connection screw. It is used together with the screwdriver handle.* |
| **Ruler** | 52143 | *The ruler is used to measure the thickness of the patient's skin before surgery and to guide the selection of the appropriate abutment length.* |
| **Double-ended dissector** | 52196 | *The Double-ended dissector is used for dissection and removal of the periosteum. The blunt side is also used for inspection of bone.* |
| **Handle with screwdriver** | 50437 | *The screwdriver handle with replaceable bits can be used together with the torque wrench. It is delivered with one screwdriver machine bit.* |
| **Insertion indicator** | 52366 | *Insertion indicator is used as a guide to visualise installation of the implant.* |
| **Abutment inserter, machine** | 51695 | *The abutment inserter is used during the single-stage surgical procedure for inserting the implant with the pre-mounted abutment, using the drill equipment. The shaft has a hexagonal collar with a shaft fitted according to ISO 1797-1.* |
| **Square fit connection** | 50386 | *The square fit connection is used for inserting the 3 and 4 mm implant with the pre-mounted implant adapter, using the drill equipment. The shaft is fitted according to ISO 1797-1.* |
| **Screwdriver, machine, 35mm** | 50384 | *The screwdriver machine bit can be used with both the screwdriver handle and the drill equipment handpiece. The bit fits all the abutment connection screws and the implant adapter screws. The shaft is fitted according to ISO 1797-1.* |

No comparator device will be used in the investigation.

## 9.4 Subject population

Patients considered for inclusion into this clinical investigation will be found among those who have already received audiological and otological evaluation and are found to be suitable candidates for BAHS treatment.

### *9.4.1 Inclusion criteria*

1. 18 years of age or older
2. Patient indicated for surgical intervention with a bone anchored hearing system
3. Signed informed consent
4. Adequate bone quality to allow for a Ponto implant insertion, as judged by the investigator, and an expected bone thickness above 5 mm, where no complications during surgery are expected
5. Skin thickness of 12 mm or less at the implant site

### *9.4.2 Exclusion criteria*

Subjects meeting any of the following criteria will not be permitted to participate in the investigation:

1. Patient undergoing re-implantation
2. Patient who are unable or unwilling to follow investigational procedures/requirements, e.g. to complete quality of life scales
3. Known condition or previous treatment that could jeopardize skin condition and wound healing over time as judged by the investigator (e.g. uncontrolled diabetes, previous radiotherapy in the area of interest)
4. Known medical condition that contraindicate surgery as judged by the investigator
5. Known and/or planned pregnancy at time of surgery
6. Any other known condition that the investigator determines could interfere with compliance or investigation assessments
7. Simultaneous participation in another clinical investigation with pharmaceutical and/or medical device which might cause interference with investigation participation

#### *9.4.2.1 Relationship of investigation population to target population*

The investigation population correlates very well to the target population of the investigational device (see section 5.5). Adult patients with all types of indicated hearing losses, whether uni- or bilateral fitted, are potentially eligible for inclusion. Patient participation is completely voluntary. Patient groups not included in the investigation relates to diseases or conditions that may compromise skin conditions, pregnancy, cognitive impairment or any other known condition that could interfere with compliance of the investigation. These patient groups may be treated outside of the study if judged suitable by the treating physician.

### *9.4.3 Number of Subjects*

A total of 50 patients will be included in the investigation. All potential subjects are already planned for treatment with a percutaneous bone-anchored hearing device and will be consecutively included in the investigation using the inclusion and exclusion criteria stated above. Bilateral surgeries are allowed. Bilaterally operated patients will account as one patient out of the 50, whereas both implant/abutment complexes will be accounted for in the implant-level analyses. The investigation will be performed at seven different sites with a maximum of 15 and an intended minimum of three subjects per site.

The investigation will be performed at the following sites:

1. Guy's and St Thomas' Hospitals, London, UK
2. Addenbroke's Hospital, Cambridge, UK
3. Queen Elizabeth Hospital, Birmingham, UK
4. Sahlgrenska University Hospital, Gothenburg, Sweden
5. Aalborg University Hospital, Aalborg, Denmark
6. Odense University Hospital, Odense, Denmark
7. Radboud University Medical Center, Nijmegen, The Netherlands

Subject inclusion is estimated to start in the last quarter of 2020, depending on when approvals from concerned ethical committees are granted. The recruitment period will be ongoing until the total number of subjects has been reached and is estimated to last for approximately 6 months. The end of the investigation is therefore expected to be around the end of the second quarter in 2022, i.e. a total study duration of 1.5 year. Since the primary endpoint is due at the 3-month visit, corresponding data will be extracted, analysed and reported as applicable, with an approximate start in the end of the third quarter in 2021. The total duration of the investigation for each subject is 12 months (from implant installation date).

Expected time schedule for investigation milestones

| | |
|---|---|
| Start of enrolment: | Q4 2020 |
| End of enrolment: | Q2 2021 |
| Primary endpoint: | Q3 2021 |
| End of study: | Q2 2022 |

### *9.4.4 Criteria and procedures for subject withdrawal or lost to follow up*

Subjects are free to discontinue participation in the investigation at any time without affecting the medical care of the subject. If a subject withdraws from the clinical investigation, the reason(s) shall be recorded. If such withdrawal is due to problems related to the investigational device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside the clinical investigation.

Withdrawal criteria:

- Unwillingness to continue participation in the study
- Loss of implant placed during the study (extrusion or elective removal)
- Patients lost to follow-up (following three documented contact attempts)

Subjects withdrawing from the investigation after implantation will not be replaced. Collected data will be considered as far as possible in analyses.

### *9.4.5 Information on vulnerable, pregnant and breastfeeding population*

In the investigation, recruitment will occur among patients already approved for a bone-anchored hearing system. Persons considered as vulnerable, e.g. due to cognitive disability or pregnancy, will not be considered for study inclusion. If pregnancy would be detected during the course of the study (after surgery), no harm is expected during the post-operative assessments and it is safe for the patient to continue throughout the investigation. The study includes no invasive procedure during follow-up. Also, no procedure-related medication will be given during follow-up unless needed for treatment of possible complications. Breastfeeding women are at no increased risk to participate in

the study.

# 10 CLINICAL INVESTIGATION PROCEDURES

The investigation-related procedures that the subjects undergo during the clinical investigation as well as the data assessed at specific visits are outlined below. All activities are performed by hospital personnel delegated by the principal investigator, e.g. surgeon, nurse or audiologist (i.e. not performed by the sponsor). After the clinical investigation is completed, all patients will be followed-up according to the clinics' routine practice.

## 10.1 Screening

The following subject demographic and other baseline characteristics will be collected at the screening visit:

- Gender
- Age (calculated from date of birth: DD-MM-YYYY)
- Ethnicity
- BMI (calculated from weight and height)
- Relevant medical and surgical history
    - e.g. skin diseases, diabetes, irradiation etc.
- Concomitant medications
    - e.g. chronic steroid use
- Smoking (history of, or current)
- Indication
    - type of hearing loss
    - monaural / bilateral
    - side(s) of surgery

## 10.2 Surgery

The surgical procedure for all patients in the investigation is described briefly in section 5.7 and in detail in the Surgical Manual and the Addendum to Surgical Manual (MONO surgical procedure).

The following information will be gathered by the surgeon in relation to the surgery:

- Duration of surgery (see section 10.2.1)
- Implant and abutment details
- Surgical instrument information (reusable surgical instruments)
- Skin thickness, incl. measurement method
- Skin punch size
- Bone quality (see section 10.2.2)
- Implant insertion torque
- No. of turns of the insertion indicator
- If manual tightening using a counter torque wrench was needed/performed?
    - If yes, no. of additional turns needed to seat the implant
- Type of anaesthesia used (general, local, or both)
- Medications given perioperatively
- Intra-operative events (see section 10.2.3)

### *10.2.1 Duration of surgery*

The length of surgery [minutes] from punch to placement of healing cap. If performed, implant stability quotient (ISQ) measurements should not be included in this time registration.

#### *10.2.2 Bone quality*

Quality of bone assessed subjectively by the investigator during surgery. Investigator will indicate quality with the following designators: 'Very soft', 'Soft', 'Medium', 'Hard' and 'Very hard'.

#### *10.2.3 Intra-operative events*

During the surgery intra-operative events and complications will be assessed by the surgeon.

Expected intra-operative events and complications includes, but are not limited to:

- Skin and bone bleedings
- Vein and sigmoid sinus exposure or damage
- Dura exposure or damage
- CSF leakage
- Insufficient bone volume or unexpected anatomy
- Angled insertion of the implant
- Re-positioning of the implant from initially chosen location (drilling at more than one site)
- Adding/using extra material at the implant site, like bone wax or Gore-tex.

**Note: If an event is judged as untoward (exceeding what is normally expected according to surgeon's judgement) it should be reported as an adverse event.**

### 10.3 Clinical investigation assessments

#### *10.3.1 Implant/abutment complex capability to provide a reliable anchorage for a sound processor after MONO surgical procedure*

The primary endpoint variable of this study ('capability to provide a reliable anchorage for a sound processor') is a composite variable depending on the outcome of five other variables:

I. Implant in situ [Implant survival: No/Yes] (see section 10.3.2);
II. Implant stable [Implant stability: No/Yes] (see section 10.3.3);
III. Absence of;
    a. adverse skin reaction (Holgers score ≥ 2) preventing use of sound processor [No/Yes] (see section 10.3.4.2);
    b. pain preventing use of sound processor on implant/abutment complex [No/Yes] (see section 10.3.6);
    c. skin overgrowth preventing use of sound processor on the implant/abutment complex [No/Yes] (see section 10.3.4.3)

For this composite endpoint to result in a positive outcome [=Yes], all involved variables need to be answered with [Yes]. If any involved variable is answered with [No], the outcome of the composite variable will be considered a failure [=No]. The rate of subjects (or implant/abutments complexes, if a subject is treated bilaterally) with a positive outcome will be used to calculate point estimates of the proportions with a two-sided 95% confidence interval. These point estimates and corresponding confidence intervals will be used to establish the expected level of implant/abutment complexes that are capable to provide a reliable anchorage (i.e. usage) for a sound processor, at the respective time point.

#### *10.3.2 Implant survival*

At each follow-up visit, the Investigator will assess whether the implant is still in situ (in place) by means of a [No/Yes] question. The rate of implant survival will be calculated from the number of

implants in situ over the number of implants that were placed. The rate of implant failure will be implicit. The reason for any failure (e.g. spontaneous, trauma etc.) will be documented.

### *10.3.3 Implant stability*

Implant stability will be assessed by means of the subjective clinical judgement of the investigator. If the implant is firmly situated in the bone and assumed to be sufficiently osseointegrated when gently manipulating the implant/abutment using the fingers, it is judged stable [Yes]. If the implant is loose, with a lack of osseointegration, the implant is judged not stable [No].

### *10.3.4 Skin assessments*

#### *10.3.4.1 Wound healing*

The investigator will assess the surgical wound and indicate if it is "completely healed" [No/Yes]. Completely healed is to be judged as a problem-free skin around the abutment. Skin dehiscence does not necessarily contradict complete healing.

#### *10.3.4.2 Holgers score*

Classification of skin reactions around skin penetrating implants will be made using the Holgers score [16]. The Holgers classification is a scale from 0 to 4 that is used to grade skin reactions. Grade 0 indicates a reaction-free area whereas 4 indicates a severe infection often requiring removal of the implant.

| **Holgers score** | |
|---|---|
| **0** | No reaction |
| **1** | Erythema with slight swelling around abutment |
| **2** | Erythema, moistness and moderate swelling |
| **3** | Erythema, moistness and moderate swelling with granulation around abutment |
| **4** | Overt signs of infection resulting in removal of implant |

#### *10.3.4.3 IPS-scale*

The IPS scale [17] is a new, consistent and uniform assessment scale for both percutaneous and transcutaneous implants for bone conduction devices. For percutaneous implants, the IPS-scale is comprising three parts: inflammation, pain, and skin height, with higher scores reflecting more severe complication. It assesses the following characteristics:

1. Inflammation:
   - Skin Integrity (intact = 0/ not intact = 1)
     - Not intact = observation of a blood crust or persistent minimal blood loss at the skin-abutment junction.
   - Erythema (none = 0/ present = 1)
   - Edema (none = 0/ present = 1)
   - Granulation tissue formation (none = 0/ present = 1)
2. Pain:
   - None = 0
   - Present, but no increase during manipulation abutment AND <6 wks present = 1
   - Present, and increase during manipulation abutment AND/OR >6 wks present = 2

- Manipulation = tightening (if needed) or tapping on the abutment

3. Skin height:
   - Normal = 0
   - Increased, but able to couple sound processor = 1
   - Above rim abutment/unable to couple sound processor =2

The ratings result in a score compiling the ratings of each parameter, i.e. $I_xP_xS_x$.

The IPS-scale offers a standardized treatment advice for each IPS-scale:

- $I_{0\text{-}1}P_0S_{0\text{-}1}$ = no treatment
- $I_0P_1S_{0\text{-}1}$ = no treatment
- $I_1P_1S_{0\text{-}1}$ = local topical treatment
- $I_{2\text{-}3}P_{0\text{-}1}S_{0\text{-}1}$ = local topical treatment
- $I_{0\text{-}4}P_2S_{0\text{-}1}$ = consider addition of systemic treatment for possible peri-implantitis
- $I_{0\text{-}4}P_{0\text{-}2}S_2$/ $I_4P_{0\text{-}1}S_0$ = consider revision/removal surgery or longer abutment (in combination with antibiotic treatment, depending on I and P-score)

It is not mandatory to follow the treatment advice, but upon analysis of the data from the study, the actual treatment given to the patients will be compared to the treatment advice as a means of evaluating the scale.

#### *10.3.4.4 Skin overgrowth*

A thickening of the skin/soft tissue surrounding the implant/abutment complex can cause problems when attaching the sound processor and may also increase the risk of feedback problem. Clinically significant skin/soft tissue overgrowth is assessed by the investigator to determine if skin overgrowth prevents the use of the sound processor [No/Yes].

### *10.3.5 Post-operative events*

Post-operative complications at implant site are assessed at all post-operative visits, with emphasis on:

- Bleeding and/or hematoma
- Hair in-growth
- Skin dehiscence around the abutment

**Note: If the event is judged as untoward (exceeding what is normally expected according to surgeon's judgement) it should be reported as an adverse event.**

### *10.3.6 Pain assessment*

The patient is asked if pain around the abutment is present [No/Yes].

If pain is present [=Yes]:

- Magnitude will be recorded using an NRS [scale from 0 = no pain to 10 = worst imaginable pain].
- Subject will also be asked if perceived level of pain prevents use of the sound processor [No/Yes], if applicable.
- Subject will be asked if pain increases with manipulation of the abutment [No/Yes]

If pain is not present [=No]:

- NRS score of 0, [0 = no pain] will be implicit.

#### *10.3.7 Numbness assessment*

The patient is asked if numbness around the abutment is present [No/Yes]. If numbness is present [=Yes], the patient is asked to judge the numbness magnitude using an NRS [scale from 0 = no numbness to 10 = complete numbness] and the circular area of numbness will be recorded as the diameter in cm of the circle, with the abutment at the centre.

#### *10.3.8 Sound processor usage*

The subject will be asked for the average number of hours per day and days per week of sound processor usage since their last visit. The question will only be asked at study visits that occur after sound processor fitting.

#### *10.3.9 Patient Reported Outcome (PRO)*

##### *10.3.9.1 Glasgow Benefit Inventory (GBI)*

The Glasgow Benefit Inventory (GBI) is a general health-related quality of life measure, developed for otorhinolaryngologic conditions. The GBI uses a scale from -100 to +100, where scores above 0 indicate improved quality of life [18]. In addition to the total GBI score, subscales for general, social and physical will be analysed. The GBI-questionnaire is to be filled in by the patient three months after surgery.

#### *10.3.10 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. The administration of this medication and all medication for adverse events must be recorded in the appropriate section of the eCRF.

### 10.4 Safety assessment

Subjects will be observed and asked about 'any health problems since last visit' during all visits in the investigation. Information that will be collected includes:

- Event description
- Start and stop dates
- Action taken due to the event
- Clinical outcome of event
- Serious: no/yes (if 'yes' more information is required)
- Device/procedure related: no/yes (if 'yes' more information is required)

All occurring adverse events will be registered, tabulated and accounted for in a safety data listing. The safety endpoint will consist of a descriptive summary, including frequency, causality, severity and duration of related events at three and 12 months after surgery. See section 19 for further reference.

## 11 MONITORING

During the investigation, representatives from Oticon Medical will have regular contacts with the investigational sites with the purpose to oversee the investigation. Monitoring activities will be performed by appointed monitors according to applicable standards (i.e. ISO14155) and internal guidance documents. The overall purposes of the monitoring are to make sure that the rights, safety and welfare of the research subjects are protected, that the reported data are accurate, complete, and verifiable from source documents, and the conduct of the clinical investigation complies with

the approved CIP, subsequent amendments (if any), applicable standards (i.e. ISO14155), and applicable regulatory and ethics committee requirements.

### 11.1 Monitoring Plan

It is estimated that there will be around three physical on-site monitoring visits at each site during the duration of the investigation: a site initiation visit (may be held remotely if training in the surgical technique has already been performed), an interim monitoring visit and a close-out visit. Should the need for an increase of on-site monitoring visits occur, e.g. for quality concerns, this will be decided on a case by case basis.

For the first two enrolled subjects at each site, 100% source data verification (i.e. comparison of data entered into the eCRF against source data) will be performed, and thereafter for every fourth enrolled subject (i.e. 25%). This level may be increased if deemed necessary. Queries will be raised within the Electronic Data Capture (EDC)-system for any discrepancies found during the monitoring activities.

The Investigator Site File (ISF) will be reviewed for accuracy and completeness throughout the investigation.

As a complement to the physical monitoring visits, centralized or remote (i.e. off-site) monitoring will be performed on an interim basis by e.g. reviewing the data entered into the EDC-system.

Further details on the extent and nature of monitoring activities as well as access to source data, and the strategy of source data verification will be outlined in a study specific, risk-based, Monitoring Plan.

### 11.2 Audits and inspections

Audits of the clinical investigation may be conducted by authorized sponsor representatives or third parties designated by the sponsor to evaluate compliance with the CIP, agreements, ISO 14155, and the applicable regulatory requirements. These audits may cover all involved parties, systems and facilities and are independent of, and separate from, routine monitoring or quality control functions. The institution's quality assurance department (or equivalent) may also visit the investigation site to perform an audit.

## 12 STATISTICAL DESIGN AND ANALYSIS

### 12.1 Study design and analysis populations

The investigation is a multinational, multicentre, prospective, single-arm investigation to establish the level of successful implant/abutment complex installations using the MONO surgical procedure. Fifty patients will be included to prospectively study the proportion of implant/abutment complexes that are performing as intended (thus capable of providing a reliable anchorage for the sound processor) three months after using the MONO surgical procedure.

Three analysis populations will be defined in the investigation, i.e. safety-, intention-to-treat- (ITT) and per-protocol- (PP) analysis populations. The data used for the safety-population analysis will include relevant safety data from all consenting subjects in the study. The ITT population will include all subjects undergoing surgery in the investigation. The PP population will include treated subjects that do not have any significant protocol deviation.

## 12.2 Sample size

The sample size in the investigation is not hypothesis-driven, but rather based on:

1. The typical size of prospective studies on surgical outcomes within the bone-anchored hearing system field.
2. The precision of the primary endpoint. The precision can be expressed as the width of the two-sided 95% confidence interval (CI).

Prospective studies from recent years were identified through literature search as part of the clinical evaluation. One study was excluded (Dumon *et al.* 2016) since it covered a period of 12 years, which cannot be considered as typical. The identified studies (Table 6) included a median of 25 patients and an average of 35 patients. For larger comparative studies the group size varied from 21 to 39 patients.

Table 6. Prospective BAHS-studies published between July 2016 and June 2019

| Year | Title | Author | implant Test (N) | implant Control (N) | Adult (N) |
|---|---|---|---|---|---|
| 2018 | Minimally Invasive Ponto Surgery Versus the Linear Incision Technique With Soft Tissue Preservation for Bone Conduction Hearing Implants: A Multicenter Randomized Controlled Trial. | Calon et al. | 33 | 30 | 63 |
| 2019 | Three-Year Clinical and Audiological Outcomes of Percutaneous Implants for Bone Conduction Devices: Comparison Between Tissue Preservation Technique and Tissue Reduction Technique. | Kruyt et al. | 25 | | 25 |
| 2017 | Bone Anchored Hearing Implant Surgery: 1 Year Follow-Up Data Shows No Effect of Hydroxyapatite Coating on Soft Tissue Reaction after Loading at 1 Week. | Høgsbro et al. | 25 | | 25 |
| 2018 | Three-year Outcomes of a Randomized Controlled Trial Comparing a 4.5-mm-Wide to a 3.75-mm-Wide Titanium Implant for Bone Conduction Hearing. | Kruyt et al. | 39 | 21 | 57 |
| 2018 | The clinical outcome and microbiological profile of bone-anchored hearing systems (BAHS) with different abutment topographies: a prospective pilot study. | Trobos et al. | 5 | 7 | 12 |
| 2018 | Wide diameter bone-anchored hearing system implants: a comparison of long-term follow-up data between tissue reduction and tissue preservation techniques. | Reznitsky et al. | 24 | 24 | 48 |
| 2017 | Baha implant as a hearing solution for single-sided deafness after retrosigmoid approach for the vestibular schwannoma: surgical results. | Boucek el al. | 5 | 11 | 16 |

The primary endpoint of this investigation is the 'capability of implant/abutment complex to provide a reliable anchorage for the sound processor at three months after MONO surgical procedure'. The primary endpoint will be presented by a point estimate (of the proportion) combined with a two-sided 95% CI, to reflect the level of successful implant/abutment complex installations using the MONO surgical procedure. Assuming a 'success rate' of 85% (conservative approach) three months after surgery, and with a confidence interval width of 20% points, the sample size needed is 50 patients. With a proportion of loadable implant/abutment complexes at three months of 95%, the resulting CI would be 11%.

Based on the above, the sample size was decided to be 50 patients.

## 12.3 Statistical methods and analytical procedures

Descriptive statistics will be used. The primary endpoint will be presented both as number and percentage, and by point estimates of the proportions combined with a two-sided 95% CI.

For secondary endpoints, the distribution of categorical and dichotomous variables will be presented both as number and percentage, although the composite variable will be presented as for the primary endpoint. Data will be presented for each time separately as well as across visits, where applicable. The distribution of continuous variables will be given as Mean, standard deviation (SD), Median, Minimum and Maximum.

For the safety endpoint, device deficiencies, adverse events and serious adverse events related to the device will be descriptively reported using frequency tables and listings.

All statistical analyses are to be explained in detail in a statistical analysis plan (SAP). Any deviations from the original analysis plan will be described in a CIP amendment, as deemed appropriate.

### 12.4 Missing data and special considerations

Missing data will not be imputed. For the primary endpoint, subjects withdrawn from the study due to loss of implant placed during the study (extrusion or elective removal) will be included in the analysis as a treatment failure (i.e. implant/abutment complex not in situ).

In case of any bilaterally implanted patient, implants will be handled as independent from each other for all implant-related variables, since this is considered more clinically relevant. Patient-variables such as patient characteristics and questionnaires will be presented on a patient-level.

No bias nor confounding factors are expected due to the single-arm design.

### 12.5 Timing of analysis

Results will be compiled and reported when all subjects have reached the primary endpoint of the study, i.e. after three months. End-of-study data will be compiled after 12 months. No other interim analysis is planned for.

## 13 DATA MANAGEMENT

All personal data collected and processed concerning the subjects participating in the investigation are protected under the Regulation (EU) 2016/679 (GDPR) and will be handled accordingly. Further, professional secrecy regarding subject information and data applies to all involved personnel, including sponsor representatives.

Names and/or other explicit personal identification information will not be collected or recorded for investigational purposes, with one crucial exception: it is the responsibility of the investigator to keep a 'Subject Identification Log' up to date, where personal identification information matches the Subject ID (see below). The 'Subject Identification Log' must be kept up to date and stored in the Investigator Site File (ISF) in a secure location with restricted access. This log will not, at any time during and after the investigation, be available to any unauthorised party, nor available in the sponsor files.

All subjects enrolled in the investigation will be provided with a Subject Identification Number (i.e. pseudonymization), consisting of a three digit code, where the leading digit represents the investigation site number, (e.g. 100 for site no. 1, 200 for site no. 2 etc.) and the two following numbers represents the consecutive subject number (e.g. 101 for the first enrolled subject at site no. 1, 202 for the second enrolled subject at site no. 2 etc.). In case of bilateral surgery, the two sides will result in two different entries in the electronic data capture (EDC) system, one for each implant/abutment complex (e.g. 101L and 101R).

## 13.1 Source documents

Source documents shall be created and maintained by the investigation site team, as per their normal clinical routine, throughout the investigation. Source documents are the original records, including but not limited to medical records, worksheets (e.g. printouts of eCRF forms), physician or nursing notes, subject questionnaires etc. Where printouts or copies of the source documentation are used for the study, these shall be signed and dated (i.e. certified) by a member of the investigation site team.

For investigation-specific variables not normally recorded in subject's medical records, a possibility to use a combined worksheet/checklist will be made available to the investigation site. These worksheets will then, if used, constitute the source for variables not entered directly in the medical records or the eCRFs. The site will store the worksheets in the ISF. The sponsor may request a copy for remote monitoring. For variables entered directly into the eCRF, the eCRF is considered the source. To ensure consistency in the recording of source data, the use of worksheets versus entering data directly into the eCRF will be defined for each site separately depending on preferred workflow (if not directly entered into the medical record).

Additionally, a source data agreement list will be used at each investigation site to define the location of source data. This list will be completed at the first interim monitoring visit at the latest.

The principal investigator will provide direct access to source data during and after the clinical investigation for monitoring, audits, and regulatory authority review and inspections, if applicable. Permission for this direct access to source documents needs to be obtained by the investigator from the subjects, hospital administration and local regulatory authorities if required by local regulations, before starting the clinical investigation.

### *13.1.1 Medical records (and equivalent)*

Unless restricted by national or local institutional regulations, the following information should be registered in subjects' medical records:

<u>At study enrolment/inclusion</u>

- Date of visit
- Study code – BC108
- Study title – *'Evaluation of clinical performance of Ponto implantation using a minimally invasive surgical technique – a prospective multicentre study'*
- Subject ID (i.e. the numerical code given at enrolment/inclusion)
- Date of enrolment/inclusion (if different from visit date)
- Information that subject has signed informed consent
- Diagnoses of relevance for the investigation – past and current

<u>At follow-up visits (incl. final visit):</u>

- Date of visit(s)
- Study code – BC108
- Visit interval (screening, surgery, 9 days, 5 weeks 3, 6, or 12 months), including a statement of study termination, if applicable
- Results of study-related assessments required to be documented in the medical records according to the 'Source data agreement list'.

- Information on adverse events (AE) – diagnosis (or signs/symptoms), start and stop dates, assessments on whether event is serious and/or related to the surgical procedure or the devices included in the investigation, and the outcome of the event.

## 13.2 Case Report Form recording and Processing

Data captured will be recorded, by the investigator and/or delegated site staff, in eCRFs by means of an EDC-system (SMART-TRIAL), provided/hosted by an external party (MEDEI ApS, Copenhagen, Denmark). The system has built-in features that enables users to be GCP and GDPR compliant. All data in relation to SMART-TRIAL is stored on secured Microsoft Azure hardware located in the EU, i.e. Dublin, Ireland. All users of the EDC system have personal accounts, accessed by two-factor authentication, allowing tracking of all data entries and changes in the system (i.e. audit trail).

All data, subject- and product-related, must be accurately recorded in a timely manner (i.e. within 5 working days) into the EDC system by the delegated site staff.

NB. For Serious Adverse Events (SAE), Serious Adverse Device Effects (SADE) stricter timelines applies, see section 19.3.1 for further reference.

All entered data must be consistent with the source documents, and if any discrepancies are found they must be corrected or explained in writing where applicable.

The patient reported outcome (PRO) instrument used in this investigation will be completed on paper forms by the subjects themselves. The forms (i.e. source documents), marked with the Subject ID, will then be transferred by manual data entry to the corresponding form in the EDC-system by an authorized member of the investigation site team.

## 13.3 Data management

Data management-related activities, e.g. data cleaning and query handling, will be performed remotely on a regular basis within the EDC-system during the investigation. Once all data for the primary endpoint (three months) or at the end of study (12 months) has been captured and recorded by the investigation site team, verified and validated by the appointed sponsor representatives, the database will be locked before any data analysis.

## 13.4 Storage of data

Readable copies of the site's eCRF data, either in printed form or in a digital format, as per the site's preference, will be archived in the ISF at the study site after study closure. Oticon Medical will not at any time point be in control of the eCRF data archived in the ISF, unless only for the purpose of delivering it to the study site.

The investigator should retain clinical investigation records (including medical records) according to regulatory requirements or for at least 10 years after completion or premature termination. The principal investigator must take measures to prevent accidental or premature destruction of these documents and at the end of the storage period, acquire a confirmation from the sponsor before proceeding with the destruction of the documentation.

The complete study database, which is a part of the TMF, will be securely stored at Oticon Medical, with restricted access. The TMF will be retained for 10 years after the last device covered by the investigational product's CE-mark has been placed on the market, or in accordance to national regulations, whichever is most stringent.

## 14 AMENDMENTS TO THE CIP

If changes to the CIP are needed, proposed amendments to the CIP shall be agreed upon between the sponsor and principal investigator, and/or the coordinating investigator. Substantial amendments should be approved by the Ethics Committee (EC) before incorporated. In addition, substantial amendments to the Patient Information and Consent Form and/or other applicable documents previously approved by the EC must be approved by the EC before they will come into effect. For non-substantial amendments, local regulations regarding notifications to EC should be followed.

## 15 DEVIATIONS FROM CLINICAL INVESTIGATION PLAN

A CIP deviation is an intentional or unintentional failure to follow the requirements of the CIP. Every effort should be made to comply with the requirements of the CIP and the Investigator, and other representatives of the investigational site team, is not allowed to deviate from the CIP, unless needed to protect the rights, safety and well-being of the subjects (i.e. emergencies). Under these circumstances, deviations from the CIP may proceed without prior approval by the Sponsor and favourable opinion from EC. Such cases should be documented and reported to the EC, as per local requirements, and to the Sponsor as soon as possible, but in no event later than 5 working days after the emergency occurred.

If other deviations occur, the Investigator should inform the monitor/clinical trial manager and make a record in the CIP Deviation Log provided in the ISF. 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 systematic 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 occur, the Sponsor has the right to initiate early termination of the study at the site(s) concerned.

At the end of the study, or in connection to a predefined interim analysis, protocol deviations will be categorized as minor or major and their consequence on analysis populations will be determined.

## 16 DEVICE ACCOUNTABILITY

The MONO Surgery kit will be delivered to the hospital as per hospital routine, or by a sponsor representative, and kept in a locked area. The sponsor will keep records of the delivered investigational devices. A device accountability log will be held on site including date of reception and date on return (if applicable).

All unused investigational devices must be returned to the sponsor when treatment of the last subject has been completed. Return of devices at the end of the investigation will be logged by sponsor in sponsor records.

The monitor will verify the accountability process at the monitoring visits.

# 17 STATEMENTS OF COMPLIANCE

The clinical investigation will be performed in consistency with the current version of the Declaration of Helsinki, ISO 14155, the Medical Device Directive (MDD) 93/42/EEC, Regulation (EU) 2017/745 (MDR) and applicable regional or national competent authority requirements as well as any additional requirements imposed by the EC.

The clinical investigation plan, including the final version of the Patient Information and Consent Form, must be approved in writing by an EC before enrolment of any subject into the investigation. The Principal Investigator is responsible for informing the EC of any amendment to the investigation plan as per local requirements.

The clinical investigation will not be commenced until approvals from the applicable EC have been received.

Any additional requirements imposed by the EC or national regulations shall be followed.

## 17.1 Insurance

The sponsor will be responsible for ensuring adequate insurance covering any injuries to the subject caused by the investigational device.

Oticon Medical has a Public and Product Liability Insurance (Policy number: DKLSCA03184), issued by CHUBB, that includes coverage of clinical trials.

## 17.2 Financing of the clinical investigation

Separate financial agreements with each study site's institution have been agreed. In brief, the study is fully sponsored by Oticon Medical AB. The investigational device is provided for free and compensation is based on the patient visit schedule at the clinics.

# 18 INFORMED CONSENT PROCESS

The principal investigator will ensure that the potential subject is given full and adequate oral and written information about the nature and purpose of the investigation, including possible risks and benefits involved. Alternatives to the treatment suggested in the CIP must be discussed to allow the potential subject to have an informed choice. Potential subjects must also be notified that they are free to decline participation in the investigation, and that they are free to discontinue at any time, without any consequences to their future care. Sufficient time will be given for consideration and the opportunity to ask questions before signing the informed consent form will be provided. The signed informed consent must be obtained before conducting any procedures specific for the investigation.

By signing the informed consent form, the subject agrees to participate in the investigation and that the results obtained may be used in authority assessments, and/or submissions for presentation or publication in scientific meetings and/or journals, with the condition that privacy and confidentiality are preserved. The subject also agrees that concerned personnel, the sponsor, external monitor (if assigned), and concerned authorities may have access to the patient's medical record to perform source data verification and other quality control measures, if applicable.

In the patient information sheet, information will be given on which legal bases, as given in Regulation (EU) 2016/649 (GDPR) [19], articles 6 and 9, that allows Oticon Medical to collect, process and archive subjects' personal data (including special categories of data, i.e. sensitive data).

Alternatively for UK citizens, the Data Protection Act 2018, which is the UK's implementation of the EU General Data Protection Regulation (GDPR), will be adhered to.

The signed original of the consent form must be filed in the ISF. A copy of the Patient information sheet including the signed informed consent form should be given to the patient.

If any new information becomes available during the investigation that possibly could influence the subjects' willingness to participate, they will be informed and asked to sign a revised informed consent, if applicable.

# 19 ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES

## 19.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational medical device.

*Note 1. This definition includes events related to the investigational medical 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 the use of investigational medical devices.*

### *19.1.1 Serious Adverse Event*

A serious adverse event (SAE) is an AE that led to any of the following:

a) death,

b) serious deterioration in the health of the subject, users or other persons as defined by one or more of the following:
   1. a life-threatening illness or injury, or
   2. a permanent impairment of a body structure or a body function including chronic diseases, or
   3. in-patient or prolonged hospitalisation, or
   4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function

c) foetal distress, foetal death or a congenital abnormality or birth defect including physical or mental impairment

*Note: Planned hospitalisation for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.*

### *19.1.2 Adverse Device Effect*

An adverse device effect (ADE) is an adverse event related to the use of an investigational medical device.

*Note 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.*
*Note 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.*

### *19.1.3 Serious Adverse Device Effect*

A serious adverse device effect (SADE) is an ADE that has resulted in any of the consequences characteristic of a serious adverse event (see section 19.1.1).

#### *19.1.3.1 Unanticipated Serious Adverse Device Effect*

An unanticipated serious adverse device effect (USADE) is a SADE which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

*Note: Anticipated Serious Adverse Device Effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis.*

## 19.2 Device deficiency

A device deficiency (DD) is defined as any inadequacy of an investigational medical device related to its identity, quality, durability, reliability, usability, safety or performance.

*Note 1: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling.*
*Note 2: This definition includes device deficiencies related to the investigational medical device or the comparator.*

Note: To distinguish between a DD and an ADE it may be useful to consider DDs as not directly affecting or involving the subject.

## 19.3 Reporting of Adverse Event(s)

All health problems*, whether judged as related to the surgery and/or the Ponto products or not, that are reported by the subject, found in medical records or found at the clinic visits must be recorded by the PI, or authorised designee, in the eCRF as an AE, preferably within 5 working days. For events judged as related, i.e. ADEs, additional information is required as specified in eCRF.

**except those defined and excluded from the investigation.*

### *19.3.1 Reporting of Serious Adverse Event / (Unanticipated) Serious Adverse Device Effect*

In addition to the information already collected and recorded for AEs/ADEs, there are more detailed information required for SAEs/SADEs/USADEs as specified in eCRF.

For SAEs/SADEs/USADEs the Investigator must:

- Record SAE/SADE/USADEs details in the eCRF immediately, but no later than **24 hours** after becoming aware of the event. An email to Oticon Medical will automatically be generated by the EDC system after investigator signing of the SAE form by the Investigator. In addition, an email shall be sent to responsible clinical trial manager (to notify the SAE/SADE/USADE).
- Follow up the initial SAE/SADE/USADEs information as soon as new information is available.
- Report SAE/SADE/USADEs to the EC according to local requirements (e.g. per event and/or annually). In multicentre investigations this may include the SAE/SADE/USADEs reported from another site; this information will be provided by Oticon Medical, if required.
- Provide Oticon Medical with all SAE/SADE/USADEs related documentation and correspondence to the EC.

#### *19.3.1.1 Reporting of Unanticipated Serious Adverse Device Effect*

The occurrence of USADEs could suggest that the clinical investigation places subjects at increased risk of harm than was to be expected beforehand. It is a sponsor obligation to handle and report USADEs to applicable authorities.

### *19.3.2 Device deficiency reporting*

The Investigator is responsible for recording the following in the CRF/eCRF, preferably within 5 working days, for all device deficiencies:

- Device deficiency details (e. g. date and description of occurrence)
- Device deficiencies that might have led to a SADE if:
  - suitable action had not been taken or
  - intervention had not been made or
  - if circumstances had been less fortunate

For device deficiencies that might have led to a SADE, the Investigator must provide Oticon Medical with detailed information in the DD-section of the eCRF and perform the applicable steps described for SAE/SADE reporting (section 19.3.1).

## 19.4 Non-reportable events

When performing a BAHS surgery, some intra- and post-operative events are more or less likely to occur (i.e. not 'untoward' per se) (see sections 10.2.3 and 10.3.5). Therefore, in this investigation, the following events will be captured in the eCRF on the applicable study visit. To avoid double-reporting, these events will not be recorded in the AE log, unless the investigator judges them to exceed the level of what is to be expected (i.e. 'untoward' per se):

During surgery;

- Drilling into veins
- Drilling into air pockets
- Dura mater exposed

Post-operative complications

- Bleeding or hematoma
- Pain or numbness
- Skin dehiscence
- Erythema
- Edema
- Granulation tissue
- Skin reactions
- Revision surgery

## 19.5 Safety event follow-up

Medical follow-up of any type of safety event will continue until the abnormality resolves, or an adequate medical explanation is apparent.

Documentation of all follow-up information regarding the AEs must be provided in the eCRF and, in accordance to the reporting requirements described above.

If the subject is withdrawn from study treatment due to an AE, the AE and the reason for withdrawal from the study is to be documented clearly in the eCRF.

### 19.6 Safety related contacts

Should the need for further guidance on safety-related issues and/or reporting be evident, the following contact details applies:

Oticon Medical

| | |
|---|---|
| Phone: | +46 31 748 61 70 (vigilance) |
| Postal address: | Oticon Medical<br>Datavägen 37B,<br>SE-436 32 Askim, Sweden |
| Mail: | QA@oticonmedical.se |

## 20 SUSPENSION OR EARLY TERMINATION OF THE CLINICAL INVESTIGATION

The investigator or sponsor may at any time terminate the clinical investigation due to circumstances related to the rights, safety and welfare of the subjects enrolled, or to the conduct of the investigation by an investigator/investigational site or sponsor, that preclude ongoing subject treatment.

If the investigation is suspended or terminated prematurely, the investigator will promptly inform the sponsor and provide the reason(s) thereof (and vice versa). The ECs concerned will also be informed promptly in writing by the investigator.

## 21 PUBLICATION POLICY

A description of this clinical investigation will be available, throughout the whole duration and onwards, on www.ClinicalTrials.gov.

When the clinical investigation is completed, even if prematurely terminated, a final report will be compiled. The results obtained in the investigation will be submitted for publication in scientific journals by the investigators, in cooperation with the Sponsor. Three-months and 1-year results could be published together or separately. The coordinating investigator will be responsible for drafting of a manuscript on the combined results in a joint, multicentre publication. Results derived from individual sites cannot be published until after the joint results are published. Privacy and confidentiality of information about each subject will be preserved in any reports and any publications of the clinical investigation data. During the course of the study, annual progress reports will be submitted to the ECs as applicable.

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# 23 SIGNED AGREEMENTS

## 23.1 Sponsor

On behalf of Oticon Medical AB I approve this clinical investigation plan.

Date and signature:

Name and title

## 23.2 Coordinating investigator

*Dr Harry Powell, Guy's and St Thomas' Hospitals, London, UK*

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 versions of the declaration of Helsinki and ISO 14155 Clinical investigation of medical devices for human subjects — Good clinical practice.

Date and signature:

Name and title

## 23.3 Principal Investigators

*Dr James Tysome, Addenbroke's Hospital, Cambridge, UK*

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 versions of the declaration of Helsinki and ISO 14155 Clinical investigation of medical devices for human subjects — Good clinical practice.

Date and signature:

Name and title

*Dr Rupan Banga, Queen Elizabeth Hospital, Birmingham, UK*

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 versions of the declaration of Helsinki and ISO 14155 Clinical investigation of medical devices for human subjects — Good clinical practice.

Date and signature:

Name and title

*Dr Måns Eeg-Olofsson, Sahlgrenska University Hospital, Gothenburg, Sweden*

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 versions of the declaration of Helsinki and ISO 14155 Clinical investigation of medical devices for human subjects — Good clinical practice.

Date and signature:

Name and title

*Dr Dan Dupont Hougaard, Aalborg University Hospital, Aalborg, Denmark*

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 versions of the declaration of Helsinki and ISO 14155 Clinical investigation of medical devices for human subjects — Good clinical practice.

Date and signature:

Name and title

*Dr Jens Højberg Wanscher, Odense University Hospital, Odense, Denmark*

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 versions of the declaration of Helsinki and ISO 14155 Clinical investigation of medical devices for human subjects — Good clinical practice.

Date and signature:

Name and title

*Dr Myrthe Hol, Radboud University Medical Center, Nijmegen, The Netherlands*

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 versions of the declaration of Helsinki and ISO 14155 Clinical investigation of medical devices for human subjects — Good clinical practice.

Date and signature:

Name and title