Official Title: A Prospective, Multicentre, Open Clinical Investigation Evaluating Clinical Performance, Safety and Patient Reported Outcomes With an Active Osseointegrated Steady-State Implant System (OSI) in Adult Subjects With Conductive Hearing Loss, Mixed Hearing Loss or Single-sided Sensorineural Deafness

NCT Number: NCT04041700

Document Date: 08 November 2019

Clinical Investigation Plan

Title: A prospective, multicentre, open clinical investigation evaluating clinical performance, safety and patient reported outcomes with an Active Osseointegrated Steady-State Implant System (OSI) in adult subjects with conductive hearing loss, mixed hearing loss or single-sided sensorineural deafness.

Short Tile:	**Clinical performance, safety and PROs of an Active Osseointegrated Steady-State Implant System (OSI)**
CIP Number:	**CBAS5751**
Version Number:	**2.0**
Date:	**08-Nov-2019**
Sponsor	**Cochlear Bone Anchored Solutions AB** **Konstruktionsvägen 14** **PO Box 82** **Mölnlycke, Sweden, SE-435 22** **+46 (0)31-792 44 00**

This clinical investigation shall be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki (1), International Standard ISO 14155 Clinical investigation of medical devices for human subjects - Good Clinical Practice (2), and any regional or national regulations, as applicable.

Manufacturer	Cochlear Limited 1 University Avenue Macquarie University New South Wales 2109 AUSTRALIA Cochlear Bone Anchored Solutions AB Konstruktionsvägen 14 PO Box 82 Mölnlycke 435 22 SWEDEN
Sponsor Organisations	Global Sponsor: Cochlear Bone Anchored Solutions AB Konstruktionsvägen 14 PO Box 82 Mölnlycke 435 22 SWEDEN Regional Sponsor: Cochlear Limited 1 University Avenue Macquarie University NSW 2109 AUSTRALIA
Coordinating Investigator	[redacted]
Clinical Research Organisation	Statistical consultants: Statistiska Konsultgruppen [redacted]
Safety Contact	[redacted]

A complete list of participating Principal Investigators' names, titles and addresses, and the names and addresses of participating institutions (sites) will be maintained by the Sponsor and will be provided as a separate Principal Investigator List. The definitive Principal Investigator list will be provided in the Clinical Investigation Report.

Investigator Agreement

Coordinating Investigator Approval and Declaration

By my signature below, I confirm my review and approval of this Clinical Investigation Plan (CIP).

I also confirm that I will strictly adhere to the requirements therein and undertake to ensure that all staff with delegated responsibilities in the conduct of this CIP have read, understood and will strictly adhere to the requirements therein. This CIP will not be implemented without prior written approval from the Ethics Committee, any applicable National Competent Authorities, and the Sponsor. If amendments to this plan become necessary, written approval by the Ethics Committee and any applicable National Competent Authorities will be obtained before the changes are clinically implemented per the amendment, except under emergency circumstances to protect the rights, safety, and well-being of subjects.

Name	**Title**
[redacted]	Coordinating Investigator
Signature	**Date**

Principal Investigator Declaration

By my signature below, I confirm that I have read, understood and will strictly adhere to the requirements therein. I undertake to ensure that all staff with delegated responsibilities in the conduct of this CIP have also read, understood and will strictly adhere to the requirements therein. This CIP will not be implemented without prior written approval from the Ethics Committee, any applicable National Competent Authorities, and the Sponsor. If amendments to this plan become necessary, written approval by the Ethics Committee and any applicable National Competent Authorities will be obtained before the changes are clinically implemented per the amendment, except under emergency circumstances to protect the rights, safety, and well-being of subjects.

Name	**Title**
[redacted]	Principal Investigator
Site Name	**Site Address**
The Royal Victorian Eye and Ear Hospital	[redacted] East Melbourne, VIC 3002 AUSTRALIA
Signature	**Date**

Principal Investigator Declaration

By my signature below, I confirm that I have read, understood and will strictly adhere to the requirements therein. I undertake to ensure that all staff with delegated responsibilities in the conduct of this CIP have also read, understood and will strictly adhere to the requirements therein. This CIP will not be implemented without prior written approval from the Ethics Committee, any applicable National Competent Authorities, and the Sponsor. If amendments to this plan become necessary, written approval by the Ethics Committee and any applicable National Competent Authorities will be obtained before the changes are clinically implemented per the amendment, except under emergency circumstances to protect the rights, safety, and well-being of subjects.

Name	**Title**
[redacted]	Principal Investigator
Site Name	**Site Address**
Sydney Cochlear Implant Centre	[redacted] Gladesville NSW 2111 AUSTRALIA
Signature	**Date**

Principal Investigator Declaration

By my signature below, I confirm that I have read, understood and will strictly adhere to the requirements therein. I undertake to ensure that all staff with delegated responsibilities in the conduct of this CIP have also read, understood and will strictly adhere to the requirements therein. This CIP will not be implemented without prior written approval from the Ethics Committee, any applicable National Competent Authorities, and the Sponsor. If amendments to this plan become necessary, written approval by the Ethics Committee and any applicable National Competent Authorities will be obtained before the changes are clinically implemented per the amendment, except under emergency circumstances to protect the rights, safety, and well-being of subjects.

Name	**Title**
[redacted]	Principal Investigator
Site Name	**Site Address**
Department of Otorhinolaryngology, Head and Neck Surgery Faculty of Medicine The Chinese University of Hong Kong	[redacted] HONG KONG SPECIAL ADMINISTRATIVE REGION OF THE PEOPLE'S REPUBLIC OF CHINA
Signature	**Date**

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1 DEFINITIONS AND ABBREVIATIONS

Term	Description
AC CROS	Air Conduction-Contralateral Routing of Signal
ADE	Adverse Device Effect
AE	Adverse Event
AESI	Adverse Event of Special Interest
APHAB	Abbreviated Profile of Hearing Aid Benefit
AuSTIN	An adaptive Australian Sentence Test in Noise
BFS	Baha Fitting Software
BCHIs	Bone Conduction Hearing Implant
CBAS	Cochlear Bone Anchored Solutions AB
CHINT	Chinese Hearing In Noise Test
CHL	Conductive Hearing Loss
CRF	Case Report Form
CRO	Contract Research Organisation
DD	Device Deficiency
EA	Electronic Assembly
EC	Ethics Committee Synonymous abbreviations/terms include: IRB (Institutional Review Board) IEC (Institutional Ethics Committee or Independent Ethics Committee) HREC (Human Research Ethics Committee)
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
FS	Fitting Software
HINT	Hearing In Noise Test
HRQoL	Health Related Quality of Life
HUI	Health Utilities Index
GCP	Good Clinical Practice
ICF	Informed Consent Form
IFU	Instruction For Use
ISO	International Organization for Standardization
ITT	Intention To Treat
MHL	Mixed Hearing Loss
MRI	Magnetic Resonance Imaging

Term	Description
OFS	Osia Fitting Software
OTE	Off-The-Ear (sound processor)
PI	Principal Investigator
PTA	Pure Tone Average
RF	Radio Frequency
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SNHL	Sensorineural hearing loss
SNR	Signal To Noise Ratio
SP	Sound Processor
SPL	Sound Pressure Level
SSD	Single-sided Sensorineural Deafness
SSQ	Speech, Spatial and Qualities of Hearing Scale
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect

2 CLINICAL INVESTIGATION SYNOPSIS

Investigation title	A prospective, multicentre, open clinical investigation evaluating clinical performance, safety and patient reported outcomes with an Active Osseointegrated Steady-State Implant System (OSI) in adult subjects with conductive hearing loss, mixed hearing loss or single-sided sensorineural deafness
Short title	Clinical performance, safety and PROs of an Active Osseointegrated Steady-State Implant System (OSI).
Investigation number	CBAS5751
Name of Investigational device(s)	The Osia 2 System includes: *The OSI200 Implant* surgically placed under the skin behind the ear. *The BI300 Implant* osseointegrated in the bone. *The Osia 2 Sound Processor (SP)* placed externally connecting to OSI200 Implant by magnetic retention.
Intended use of Investigational device(s)	The Cochlear Osia 2 System is indicated for patients with conductive hearing loss (CHL), mixed hearing loss (MHL) and single-sided sensorineural deafness (SSD). Patients should have sufficient bone quality and quantity to support successful implant placement. The Osia 2 System is indicated for patients with up to 55 dB SNHL. The regulatory status is pre-market.
Name and description of comparator device/product(s)	Not applicable
Expected start date (first subject consented)	Aug 2019
Expected enrolment period	4 - 6 months
Expected duration per subject	6 months
Expected total duration of the clinical investigation	12 - 15 months
Number of subjects planned	30 subjects
Number of investigational sites planned	3 sites
Inclusion criteria	1. Subject with CHL or MHL in the ear to be implanted. **Bone conduction thresholds** with pure tone average (PTA4; mean of 0.5, 1, 2 and 4 kHz) of ≤ 55 dB SNHL. OR

	Subject with SSD who is a candidate for Baha surgery. **Air conduction thresholds** with a pure tone average PTA4 (mean of 0.5, 1, 2 and 3 kHz) of ≤ 20 dB SNHL in the good ear OR subject who is indicated for an AC CROS (Air Conduction-Contralateral Routing of Signal) but—for some reason—cannot or will not use an AC CROS. 2. Adult subjects (18 years or older). 3. Previous experience from amplified sound through properly fitted amplification (for example but not limited to Hearing aid, CROS device, Bone conduction hearing device on softband). 4. Candidate is a fluent speaker in the language used to assess speech perception performance. 5. Willing and able to provide written informed consent.
Exclusion criteria	1. Uncontrolled diabetes as judged by the investigator. 2. Condition that could jeopardise osseointegration and/or wound healing (e.g. osteoporosis, psoriasis, long-term systemic use of corticosteroids) or condition that may have an impact on the outcome of the investigation as judged by the investigator. 3. Insufficient bone quality and quantity to support successful implant placement. 4. Previous surgery and/or implantation with any bone conduction/active device on the side to be implanted, which may jeopardise the implantation and use of the Osia 2 system, as judged by the investigator. 5. Use of ototoxic drugs that could be harmful to the hearing, as judged by the investigator. 6. Unable to follow investigational procedures, e.g. to complete quality of life scales, or unwilling to comply with the requirements of the clinical investigation as determined by the investigator. 7. Condition with a likely negative progression and/or with expected relapses jeopardising general wellbeing and health-related quality of life as judged by the investigator. 8. Subject that has received radiotherapy in the area of implantation or is planned for such radiotherapy during the study period. 9. Investigator site personnel directly affiliated with this study and/or their immediate families; immediate family is defined as a spouse, parent, child, or sibling. 10. Cochlear employees or employees of Contract Research Organisations or contractors engaged by Cochlear for the purposes of this investigation 11. Currently participating, or participated within the last 30 days, in another interventional clinical investigation involving an investigational drug or device.

Objectives and Outcome measures	
Primary Objective	**Outcome measure**
To compare hearing performance between the Investigational device and the unaided hearing.	At 3 months compared to preoperative • Thresholds audiometry, free-field [PTA4, Mean of 0.5, 1, 2 and 4 kHz]. • Adaptive speech in noise [signal-to-noise ratio, 50% speech understanding].
Secondary Objectives	**Outcome measures**
To compare hearing performance between the Investigational device and the unaided hearing.	At fitting and 6 months compared to preoperative. • Thresholds audiometry, free-field [PTA4, Mean of 0.5, 1, 2 and 4 kHz]. • Adaptive speech in noise [signal-to-noise ratio, 50% speech understanding]. At fitting, 3 and 6 months compared to preoperative. • Thresholds audiometry, free-field [0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0 and 8.0 kHz]. • Speech in quiet [% correctly perceived words at 50dB, 65dB and 80dB SPL].
To compare the self-reported assessments of hearing outcome between the Investigational device and the unaided hearing.	At 3 and 6 months compared to preoperative. • Abbreviated Profile of Hearing Aid Benefit (APHAB). • Speech, Spatial and Qualities of Hearing Scale (SSQ).
To compare health-related quality of life (HRQoL) between the Investigational device and the preoperative hearing situation.	At 3 and 6 months compared to preoperative. • Health Utilities Index (HUI).
To collect surgical information.	• Soft tissue thickness (mm) • Type of anesthesia (general/local) • Bone polishing/removal at the actuator site (yes/no) • BI300 Implant length (3mm/4mm) • Location of BI300 Implant (mm between the ear canal and the center of the actuator). • Soft tissue reduction (yes/no) • Surgical incision type (examples; C-shaped/S-shaped/straight) • Location of the surgical incision in relation to the actuator (anterior/posterior) • Estimated length of the surgical incision (mm) • Placement of the coil (periosteal pocket (under periosteum)/on top of periosteum/on top of muscle) • Surgery time (time between first incision to last suture)

To collect information about the usability.	• Magnet choice • Sound Processor retention • Sound Processor wearing comfort • Use of SoftWear pad • Daily use • Daily streaming time • Battery lifetime
To compare hearing performance between the Investigational device and a Baha 5 Power Sound Processor on a Baha Softband (preoperative).	At fitting, 3 and 6 months compared to preoperative. • Thresholds audiometry, free-field [PTA4, Mean of 0.5, 1, 2 and 4 kHz]. • Thresholds audiometry, free-field [0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0 and 8.0 kHz]. • Adaptive speech in noise [signal-to-noise ratio, 50% speech understanding]. • Speech in quiet [% correctly perceived words at 50dB, 65dB and 80dB SPL]. • BC Direct [0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0 and 6.0 kHz].
Tertiary Objectives	**Outcome measures**
To measure hearing performance preoperatively with a current hearing aid (if used by the patient). To perform feedback measurements for the Investigational device	• Adaptive speech in noise [signal-to-noise ratio, 50% speech understanding]. • Feedback measurements data
Safety Objective	**Safety Outcome measures**
Primary safety analysis at 3 months post-surgery	
Implant site evaluation	Numbness will be collected from Suture removal and onwards.
Adverse events	Information will be collected from Surgery and onwards.
Device deficiency	Information will be collected from Surgery and onwards.
Concomitant medication	Information will be collected from Surgery and onwards.

3 SCHEDULE OF EVENTS

	Screening And Baseline	Surgery	Suture removal	Fitting	Follow up 6W	Follow up 3M	Follow up 6M
Timing of visit		**0**	**2W**	**4W**	**6W**	**3M**	**6M**
Visit window (±)			**±5D**	**±1W**	**± 1W**	**± 2W**	**± 3W**
Procedures							
Written informed consent	X						
Demographics	X						
Eligibility	X						
Medical history	X						
Hearing history	X						
Device history	X						
Audiogram	X[a]						
Soft tissue thickness	X						
Surgery		X[b]					
Suture removal			X				
Sound processor fitting	X[c]			X	X[d]	X[d]	X[d]
Microphone placement				X			
Fine tuning				X	X[d]	X[d]	X[d]
Feedback measurements				X	X[e]	X[e]	X[e]
Coil-to-coil measurements				X	X[e]	X[e]	X[e]
BC Direct	X[f]			X	X[e]	X[e]	X[e]
Free field thresholds	X[f, g]			X		X	X
Speech recognition in quiet	X[f, g]			X		X	X
Speech recognition in noise	X[f, g, h]			X		X	X
APHAB	X[g]					X	X
SSQ	X[g]					X	X
HUI	X[h]					X	X
Usability				X[i]	X[i]	X[i]	X[i]

	Screening And Baseline	Surgery	Suture removal	Fitting	Follow up 6W	Follow up 3M	Follow up 6M
Timing of visit		**0**	**2W**	**4W**	**6W**	**3M**	**6M**
Visit window (±)			**±5D**	**±1W**	**± 1W**	**± 2W**	**± 3W**
Numbness			X	X	X	X	X
Device exposure [j]		X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X
Device Deficiencies		X		X	X	X	X
Concomitant therapies	X	X	X	X	X	X	X
Extra visits as needed							

Abbreviations: BC, Bone Conduction; APHAB, Abbreviated Profile of Hearing Aid Benefit; SSQ, Speech, Spatial and Qualities of Hearing Scale; HUI, Health Utilities Index

[a] An audiogram not older than 6 months can be used if it contains all the required frequencies (250, 500, 750, 1000, 1500, 2000, 3000, 4000, 6000 and 8000Hz).

[b] Surgical variables: Surgery time, Bone polishing/removal at the actuator site, BI300 Implant length, Location of BI300 Implant, Type of anesthesia, Soft tissue reduction, Surgical incision type, Length of the surgical incision, Placement of the coil, Soft tissue thickenss, Location of surgical incision

[c] Should be performed with Baha 5 Power at Screening and Baseline

[d] Should be done if needed.

[e] Should be performed at each occasion the software is being used to fit or fine tune the device

[f] Baha 5 Power Sound Processor on Baha Softband.

[g] Unaided.

[h] In a preoperative hearing situation

[i] Usability: Magnet choice, Sound Processor retention, Sound Processor wearing comfort, Daily use, Daily streaming, Battery life time, Use of SoftWear pad

[j] "Device exposure" is to collect information about for how long the subject is exposed to the Osia 2 Sound Processor and Osia 2 Implant. Data is summarized from other case report form pages.

4 BACKGROUND INFORMATION AND RATIONALE

4.1 Introduction

Developed in the late 1970's, Bone Conduction hearing implant (BCHI) systems are a well-established treatment modality that has proven to be a safe and effective way of providing hearing in patients with CHL, MHL or SSD. The Osia® System is the latest addition to Cochlear's BCHI Systems – combining the distinct benefits of the Baha® Connect and the Baha Attract Systems.

4.1.1 The Baha Systems

The Cochlear™ Baha bone conduction systems offer two ways to transmit vibrations from the external sound processor to the osseointegrated implant:

The Baha Connect System uses a skin-penetrating abutment that provides a direct pathway for transmission of sound vibrations from the sound processor (SP) to the osseointegrated implant. The Baha Connect System thereby offers optimal efficiency of sound transmission via direct bone conduction. However, the skin-penetrating abutment of the Baha Connect System is seen as a barrier for many candidates and requires daily cleaning of the skin around the abutment in order to maintain a reaction-free implant site.

The passive transcutaneous Baha Attract System uses a magnetic connection through intact skin. This offers the advantages over skin-penetrating systems by eliminating the daily cleaning, reduction in reported adverse skin reactions of the implant site and is perceived as more cosmetically appealing by many subjects. However, the Baha Attract System offers less efficient bone conduction (especially at high frequencies) due to attenuation of sound vibrations through the intact skin that separates the external transducer from the osseointegrated implant.

Both Baha Systems make use of the same external SPs and the same osseointegrated Implant (BI300). Both systems have been proven to be safe and effective through years of clinical use and data from clinical investigation (3) (4) (5).

4.1.2 The Osia system

The Osia® System is an Active Osseointegrated Steady-State Implant System (OSI) where the whole actuator/transducer (vibrating unit) is implanted and fixed to the same osseointegrated implant (BI300) as the Baha Systems. The system is developed to combine the benefits of a skin-penetrating system (direct bone conduction) combined with the benefits of a non-skin-penetrating system (less need for maintenance care, cosmetic advantages, etc.). Compared to the passive transcutaneous Baha Attract System, the Osia System provides a more efficient transmission of sound, especially in the high frequency range, as the implantable transducer eliminates the attenuation of sound vibrations through the soft tissue that is inherent to the passive system. With the Osia System it is also possible to position the transducer closer to the ear canal, which may further improve audiological outcomes.

The Osia System is intended to compensate for CHL, MHL, or SSD by transmitting amplified acoustic signals to the cochlea through mechanical vibration of the skull bone. It is indicated

for recipients with a fitting range of up to 55 dB SNHL (for mixed hearing loss), which is in the same fitting range as the Baha 5 Power Sound Processor.

4.1.2.1 The Osia 2 System

The Osia 2 System is a further development of its predecessor device, the Osia System, which received regulatory approval (CE-mark) in 2018.

The design modifications primarily consist in a more robust implant with a less complex surgical procedure, and a more advanced and aesthetically appealing sound processor. None of the changes that have been made to the Implant or SP are anticipated to significantly alter the safety or performance of the system.

The predecessor device (the Osia System) has been tested in a prospective multicentre clinical investigation, and has, at the time of writing this CIP, been implanted in over 100 recipients. Results show that the system provides good audiological performance and patient-reported outcomes in patients with CHL, MHL and SSD and that complications are few. The following section(s) describe the findings from both non-clinical and clinical data supporting the safe and effective use of the Osia 2 System.

4.2 Findings of Previous Nonclinical and Clinical Studies

4.2.1 Nonclinical Data

The OSI200 Implant has been designed in a way to allow for less complex surgical procedure, involving fewer surgical instruments and less bone excavation during implantation than for the predecessor OSI100 Implant, and has been tested and reported (6). The OSI200 implant is also more robust in its design and is anticipated to perform in a similar manner as its predecessor device, with a safety profile equal to, or better than, the OSI100 Implant (7).

The Osia 2 SP has the same intended performance but offers an improvement over the predecessor sound processor with regards to size, weight, signal processing and wireless functionality. Results from technical verification and validation activities are described in the currently released Investigator's Brochure (7).

4.2.2 Clinical Data

The objective of this clinical investigation is to gather clinical data on the Osia 2 System; as such, no in-patient clinical data is currently available for the Osia 2 System itself. However, the predecessor Osia System is currently (at the time of this final CIP) being tested in a prospective, multicentre clinical investigation including 51 subjects with CHL, MHL (up to 55 dB SNHL) or SSD (see section 4.2.2.1). In addition to clinical data on the predecessor, the Osia 2 SP and the predecessor SP are (by the time of finalising this CIP) being compared in patients already implanted with the precursor Implant (OSI100). Both the Osia 2 SP and the OSI200 Implant are also being clinically tested using an Osia Simulation model (section 4.2.2.2)

4.2.2.1 Multicentre Clinical Investigation with the Osia System

By the time of this final CIP safety and performance of the predecessor device Osia System is being tested in a prospective, multicentre clinical investigation CBAS5539 (ClinicalTrials.gov Identifier NCT 03086135) including 51 adults with CHL (n=14), MHL (n=23), or SSD (n=14). Subjects were unilaterally (n=49), or bilaterally (n=2) implanted and serve as their own controls (i.e. pre-operative unaided hearing vs. aided hearing with the Osia System). All subjects have passed the 6 months follow-up and, as such, have completed the primary efficacy (3 months) and safety (6 months) endpoints, with data collection continuing until study completion at 12 months (8).

4.2.2.1.1 Performance

The results from the clinical investigation demonstrate the following benefits for subjects with CHL, MHL and SSD with regards to hearing performance and health related quality of life.

The Osia System provided statistically significant improvements in hearing performance compared to the unaided condition with an improvement in hearing thresholds (PTA4, mean of 0.5, 1, 2, and 4 kHz) of 24.9 dB (SD 9.5 dB, range -50 to -6 dB, $p<0.0001$), speech recognition in quiet at 50, 65 and 80 dB SPL of 37.9 % (SD 25.2, range -40.0 to 80.0 %), 59.8 % (SD 27.1, range -5.0 to 100.0 %) and 31.7 % (SD 32.0, range -4.0 to 100.0 %), respectively, and adaptive speech in noise (SNR) of -13.3 dB (SD 8.1, range -47.2 to 0.6 dB, $p<0.0001$).

All SSQ parameters (Total, Speech, Spatial, and Quality) showed statistically significant improvements ($p<0.0001$) and APHAB scores showed significant improvements ($p<0.0001$) for the subscales Ease of Communication (EC), Background Noise (BN), Reverberation (RV), and the Global score. Health status and health related quality of life, measured with HUI3, showed statistically significant improvements for the parameters Comprehensive health state ($p=0.035$) and Hearing attribute ($p=0.0014$).

Comfort with the use of the Osia System, measured using a visual analogue scale where 0% was defined as no comfort at all and 100% as most comfortable imaginable, showed a total mean comfort of 81% at 3 months and the mean reported daily use was 10.5 hours/day (SD 4.3, range 1.0-18.0 hours/day).

Analysis of the separate subgroups (CHL/MHL and SSD) showed similar trends as for the entire population.

4.2.2.1.2 Safety

In total 68 *Adverse Events* (AEs) were reported during the first six months of the clinical investigation, whereof thirty-three (33) were judged as possibly, probably or causally related to the study device and/or procedure. Most of the AEs were reported as mild and related to post-operative pain or transient irritation/swelling.

Three (3) *Serious Adverse Events* (SAEs) were reported within the first six months and within the same subject. Two (2) of these SAEs were unrelated to the study device and/or procedure, and one (1) was related to the surgical procedure: One Osia Implant was removed due to wound infection starting shortly after surgery. There were no device-related SAEs recorded during this time period.

Seventy-one (71) *Device Deficiencies (DDs)* have been reported (to date); However, none of the DDs were related to the Implant (Fitting Software: 46.5%; Sound Processor: 41%; User Manual: 8.5%; Broken safety line: 4%)

4.2.2.2 Ongoing Clinical Investigation: Osia 2 System

The Osia 2 SP, which is compatible with both the OSI100 and OSI200 Implants, is currently being tested in two different clinical investigations. The first investigation CBAS5731 (ClinicalTrials.gov Identifier NCT NCT03848910 is designed to compare hearing performance and patient preference of the Osia 2 SP to the Osia SP in patients (n=11) that have completed the Osia System multicentre clinical investigation (i.e. that have already been implanted with the OSI100 Implant). The other investigation CBAS5749 compares hearing performance of the Osia 2 System to its predecessor device using a validated simulation model. In this investigation, audiological outcomes with the different combinations of the Osia System sound processors and implants are tested on actual Baha Connect users, which allows within-subject comparisons of the different SPs and Implants.

While the final results from these clinical investigations are not yet available at the time of finalising this clinical investigation plan (will be finalised before the start of this clinical investigation), preliminary data suggests good outcomes with the Investigational device.

4.3 Study Rationale

The Osia 2 System is a further development of its predecessor device (the Osia System) which has been regulatory approved in Europe and has been proven safe and effective, providing significantly improved objective and subjective hearing outcomes and health-related quality of life in subjects with CHL, MHL or SSD when compared to the pre-operative unaided condition. Currently, there is nothing that would contradict the safety and performance of the Osia 2 System; however, as with any surgical procedure, Osia surgery is not entirely free of risks.

The clinical investigation on the Osia System (predecessor device) showed no serious adverse events or device deficiencies related to the Implant (OSI100) and most adverse events that were judged as possibly, probably or causally related to the procedure/device occurred within the first 1 to 3 months and were related to the surgical procedure (n=33). As mentioned in section 4.2.1, the design of the OSI200 Implant allows for a shorter, less complex surgical procedure with fewer surgical instruments, less bone excavation; as such, it is anticipated that any risks related to the surgical procedure will be similar or less than for the OSI100 Implant.

The Osia 2 System also has the same performance requirements as the first Osia System, but includes a sound processor with added functionality, wireless connectivity and improved aesthetics, all of which are believed to provide added benefit to the user.

The rationale for conducting this clinical investigation is to gather clinical data on patients implanted with the OSI200 Implant. While the non-clinical and clinical data all indicate that the Osia 2 System will perform as intended and provide a bone conduction hearing implant (BCHI) system with a similar, or improved, safety profile as its CE-marked predecessor device, which is currently being used by more than one hundred recipients world-wide, it is of utmost interest to assess the performance and safety of the Osia 2 System when used as intended. The study method proposed in this clinical investigation plan is considered relevant to the intended use of the Investigational device and the data collection period/intervals reflects potential safety

concerns identified in risk management activities and as reported in the multicentre clinical study on the predecessor device.

The method to evaluate objective and subject hearing performance is based on the same protocol as for the multicentre clinical study on the first generation Osia System. Even though patients included in the clinical study will serve as their own control, by adopting the same means of evaluating performance (i.e. same performance variables) an indirect comparison to the predecessor device may be made as a means to ensure State-of-the-art performance.

5 MEDICAL DEVICE INFORMATION

5.1 Identity and Description of the Investigational Device

The Osia 2 System is an Active Osseointegrated Steady-state Implant System that vibrates the skull-bone and subsequently the cochlea, bypassing the impaired ear canal and/or middle ear of individuals with conductive hearing loss, mixed hearing loss, or leading the vibrations to the contralateral cochlea for single-sided sensorineural deafness (SSD). The system was built to combine the distinct advantages of the percutaneous (efficient bone conduction) and transcutaneous (no skin penetration) Baha systems, with a fitting range of up to 55dB SNHL.

The system consists of internal and external parts. The internal part is an implant made up of a receiver coil and the actuator (vibrator) (see section 5.1.1) which is surgically implanted on the skull bone. The external part is a sound processor, worn off-the-ear (OTE), which picks up the sound from the environment and sends, after processing, the information to the implant via a transcutaneous inductive link. Each system is configured to meet an individual's impaired hearing needs, using dedicated fitting software.

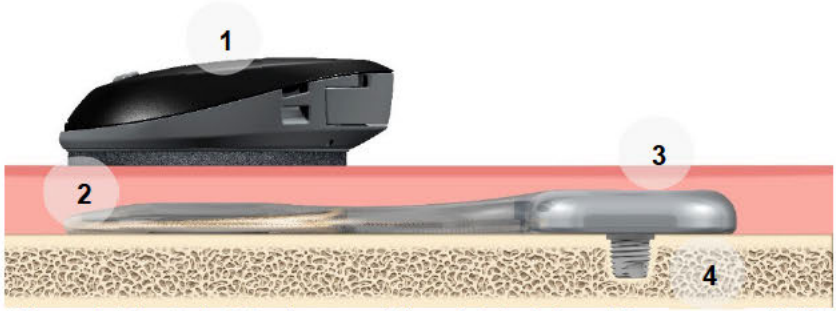

Figure 1: The Osia 2 System consisting of Osia 2 Sound Processor and OIS200 Implant.

In normal operation, the Osia 2 System functions as follows (see figure 1):

1. The external sound processor captures and digitally processes sound.
2. The sound processor transmits power and digital information to the implant.
3. The implant actuator converts the digital information into an electric analog signal, which creates vibrations.
4. The vibrations are transmitted to the skull bone through the BI300 Implant.

The regulatory classification of the system is expected to be Class AIMD in the EU and Class II in the US. The instruments of the Osia 2 System that have previously been CE marked and FDA cleared for the current Baha or Cochlear Implant (CI) systems maintain their current classification. The BI300 Implant will also maintain its classification in the EU (Class IIb), in the US (Class II), in Australia (Class II) and in Hong Kong (Class III).

5.1.1 The OSI200 Implant

The OSI200 Implant is a single use device intended for long term implantation under the skin in the mastoid region of either side of the head. It is made up of the receiver coli, magnet assembly and the implant body (Figure 2).

The radio frequency (RF) receiver coil receives power and data for the implant when it is inductively coupled to a similar coil in the external SP. The magnet assembly ensures that the SP is firmly attached and correctly aligned with the receiver coil. The implant body encapsulates the electronic assembly (EA) and actuator components. The EA receives the signal from the RF receiver coil and processes it accordingly, using the data received to drive the actuator. The actuator converts the electrical signal into an amplified mechanical stimulation and transmits it to the mastoid bone through the osseointegrated BI300 implant. The entire implant assembly is enclosed within a silicone overmould. The overmould material (MED-4860) is a medical grade, biocompatible silicone suitable for long term implantation. The OSI200 Implant attaches to the skull bone via a BI300 Implant (ossointegrating titanium fixture).

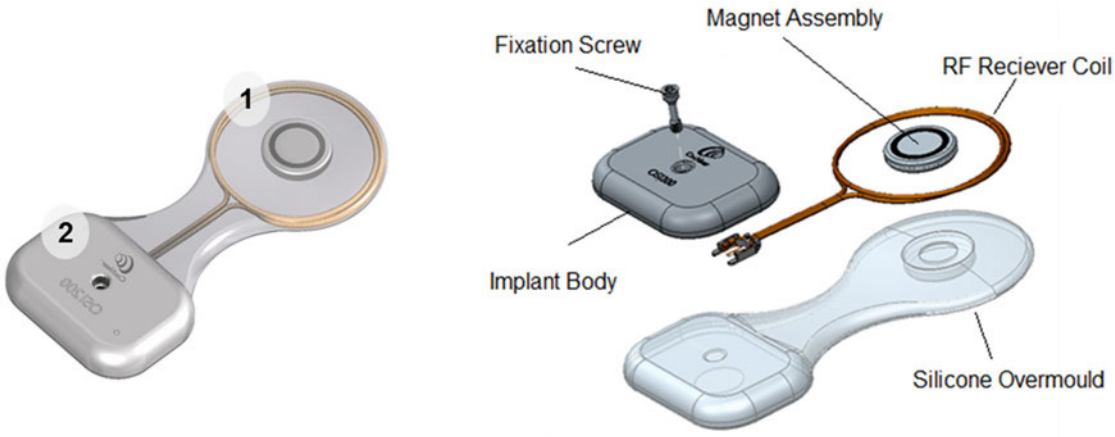

Figure 2. Left: OSI200 Implant with the Receiver coil and magnet assembly (1) and the Implant body with actuator and electronic assembly (2); Right: The different subassemblies of the OSI200 Implant.

5.1.2 The Osia 2 Sound Processor (Osia 2 SP)

The Osia 2 SP is a button-type SP, worn off-the-ear (OTE) (Figure 3), to be used with the OSI200 Implant.

During use, the Osia 2 SP is in contact with the skin or hair and is kept in place by two magnets, one external magnet in the Osia 2 SP and one internal magnet in the OSI200 Implant. The

intended use is daily and as long as the subjects feels they need to have amplification, which could mean a full day.

The Osia 2 SP is compatible with the Cochlear wireless accessories available on the market as well as various other accessories like Safety line and SoftWear pad. It is also compatible with iPhone via Bluetooth Low Energy enabling the use of apps and streaming. The subjects will be able to choose from five different front colors for their SP.

The Osia 2 SP is powered by one battery which is expected to be enough for one full day of use. The Osia 2 SP is further described in the Cochlear Osia 2 Sound Processor User Manual.

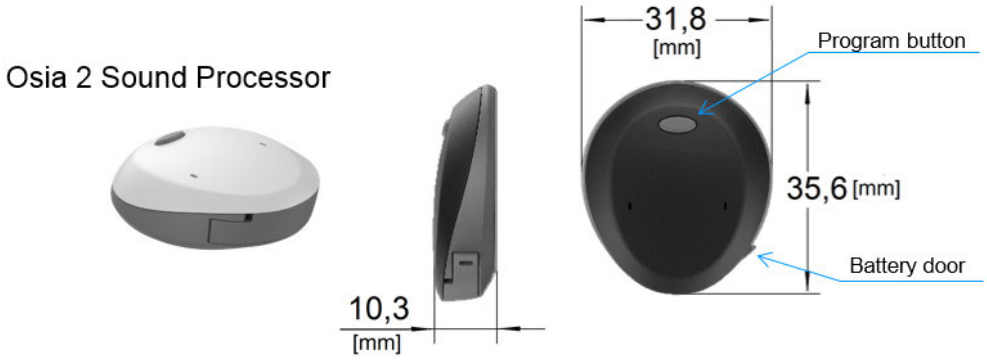

Figure 3. The Osia 2 Sound Processor.

5.1.3 Osia 2 Sound Processor Magnets

Sound Processor Magnets for the SP comes in 4 different strengths; 1 being the weakest and 4 the strongest.

5.1.4 BI300 Implant

The Osia 2 System uses the same osseointegrated BI300 Implant for anchorage in the bone as in existing first Osia System, Baha Connect and Baha Attract systems. The BI300 Implant is 4.5 mm in diameter and comes in two different lengths, 4 mm and 3 mm, and is made of titanium. The surface is moderately roughened (TiOblast™) on its intraosseous parts. A cover screw (92136) is available in case of the need to close the surgical incision after implanting the BI300 without attaching the actual OSI200 Implant.

The OSI200 Implant body attaches to the internal connection of the BI300 Implant using a fixation screw.

Figure 4. BI300 Implant 4 mm

Table 1. List of parts of the Investigational device.

Name	Description	Part Number
Cochlear™ Osia® 2 Sound Processor Kit	One SP base, all five covers, one programming front and one inner case and Tamperproof tool in one package.	P1233400
Cochlear™ Osia® OSI200 Implant	OSI200 Implant	P1170466
Cochlear™ Osia® 2 Sound Processor Magnet pack	Strength 1-4	P1343790 (strength 1, 4 pcs) P1343791 (strength 2&3, 1+1 pcs) P1343793 (strength 4, 4 pcs)
BI300 Implant	3 and 4 mm	92128, 92129

5.1.5 Surgery

The Osia OSI200 Implant is surgically implanted under the skin behind the ear.

The surgical procedure includes the following:

1. Preparation of implant site
2. Coil pocket creation and incision
3. BI300 Implant placement
4. OSI200 Implant placement
5. Closure

The surgical procedure is further described in section 7.3.2.1 and in the Cochlear Osia OSI200 Implant Physicians Guide (9). The physician's guide is intended for surgical staff involved in implanting the device. Surgeons implanting the device should be experienced in cochlear implant and/or bone conduction implant surgery or have received appropriate information and/or training to perform the surgery. The physician's guide also includes important information on MRI, indications, contraindications, adverse effects, warnings and precautions.

5.1.6 Training

The Sponsor will organise an initiation visit during which the handling of the medical device(s), the clinical investigation plan, procedures including the informed consent process, instructions regarding case report form (CRF) completion and any other matters relating to running the investigation at the site will be discussed with the investigators and queries clarified.

The principal investigator will ensure that appropriate training relevant to the study is given to the medical, nursing and other staff involved at the clinic and that new information of relevance to the performance of this study is forwarded to the staff involved.

Each investigator performing the surgery in the clinical investigation will be trained in the surgical procedures for the investigational device before they start any implantation.

5.1.7 Manufacturer of investigational device(s)

Cochlear Limited, Sydney, Australia is the legal manufacturer for everything in the Osia 2 system, except the BI300 implant.

Cochlear Bone Anchored Solutions AB, Mölnlycke, Sweden is the legal manufacturer for the BI300 Implant.

Table 2. List of the manufacturers for the different parts of the Osia 2 System.

Identity	Name and Address	Scope / Activity
Legal Manufacturer	Cochlear Limited 1 University Avenue Macquarie University New South Wales 2109 Australia	Everything in the Osia 2 system except BI300 Implant
Legal Manufacturer	Cochlear Bone Anchored Solutions Konstruktionsvägen 14 435 33 Mölnlycke Sweden	BI300 Implant

5.2 Identity and Description of the Reference device

The Baha 5 Power Sound Processor (95471) on a Baha Softband (95784) will be used at Baseline for the subject, before the surgery visit, to measure preoperative Sound Processor performance and to prepare the subject for the postoperative hearing situation.

The legal manufacturer for the Baha 5 Power Sound Processor (95471) on a Softband is Cochlear Bone Anchored Solutions, Mölnlycke, Sweden.

5.3 Accessory Device Requirements

5.3.1 Accessories

In the study the following other approved accessories will be distributed by Cochlear:

- Cochlear Nucleus safety line (Long) (P742062), Nucleus Safety Line (Short Double Loop) – Black, white and brown (P743011, P743013 and P743015). Can be used to secure the Osia 2 SP in case of loss of magnetic retention.

- Programming Cables CS45 long, blue and red (P1343629 and P1343630).
- SoftWear pads (ID P793402).
- Tool kit (Magnet tool, tamperproof tool & programming cover)
- Magnet packs (Size 1 to 4 magnets)

5.3.2 The Osia Fitting Software

To adjust and fit the Osia 2 SP to each recipient needs, programming software will be used— the Osia Fitting Software (OFS) with the currently released version at the time of the clinical study. Communication between the computer-based software and the sound processor is achieved using a Hi-Pro 2 programming unit. The OFS 2 is a further developed fitting software, based on the first Osia fitting Software (OFS 1.0) and Baha Fitting Software (BFS 5.4)

Cochlear Limited, Sydney, Australia is the legal manufacturer for the OFS.

5.3.3 The Baha Fitting Software

To adjust and fit the Baha 5 Power SP to each recipient needs at the Screening and Baseline visit, a programming software will be used— Baha Fitting Software (BFS 5.0).

Cochlear Bone Anchored Solutions, Mölnlycke, Sweden is the legal manufacturer for the BFS.

5.3.4 Surgical instruments

The surgical procedure for the Osia 2 System combines steps of the recommended surgical procedure for implantation of the BI300 Implant and the BIM400 Implant Magnet of the Baha Attract System. Hence, Osia surgery reuses existing surgical tools for Baha surgery. There are only one surgical tool and one template that are specific to the Osia 2 System. Table 3 lists the recommended surgical instruments.

The Bone Bed Indicator is a reusable instrument to be used to verify the clearance between the actuator bottom plane and the bone surface. It is hand tightened to the BI300 Implant and then turned clockwise around to check the clearance of the surrounding area. The OSI200 Implant Template is a single-use sterile marking template to be used during marking of the skin and the bone during surgery to indicate placement of the OSI200 Implant.

Cochlear Limited, Sydney, Australia is the legal manufacturer for the Bone Bed Indicator and the Implant Template.

Cochlear Bone Anchored Solutions, Mölnlycke, Sweden is the legal manufacturer for all existing instruments relating to the BI300, which are already on the market.

Table 3: List of surgical instruments.

Instrument	Description	Part Number
New non-approved surgical instruments		
Osia 2 Specific Reusable Instruments	OSI Bone Bed Indicator	P1469690
Osia 2 specific Single Use Instruments	OSI200 Implant Template (Sterile, single use)	P1291019
Existing approved surgical instruments		
Cochlear Baha Reusable Instruments	Screwdriver Unigrip 95 mm	90469
	Multi wrench with ISO adapter	92143
	Machine Screwdriver Unigrip 25 mm	90381
	Implant inserter	92142
	Drill indicator	91116
	Baha ruler	93339
Cochlear Baha Single Use Instruments (sterile)	Conical guide drill 3+4 mm	93363
	Widening drill 3 mm with countersink	92140
	Widening drill 4 mm with countersink	92141

Complete information on the Osia 2 surgical instruments is found in the Cochlear Osia OSI200 Implant Physician's Guide.

6 OBJECTIVES

6.1 Primary Objective

Primary Objective	Outcome measure
To compare hearing performance between the Investigational device and the unaided hearing.	<u>At 3 months compared to preoperative</u> • Thresholds audiometry, free-field [PTA4, Mean of 0.5, 1, 2 and 4 kHz]. • Adaptive speech in noise [signal-to-noise ratio, 50% speech understanding].

6.2 Secondary Objective

Secondary Objectives	Outcome measures
To compare hearing performance between the Investigation device and the unaided hearing.	At fitting and 6 months compared to preoperative. • Thresholds audiometry, free-field [PTA4, Mean of 0.5, 1, 2 and 4 kHz]. • Adaptive speech in noise [signal-to-noise ratio, 50% speech understanding]. At fitting, 3 and 6 months compared to preoperative. • Thresholds audiometry, free-field [0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0 and 8.0 kHz]. • Speech in quiet [% correctly perceived words at 50dB, 65dB and 80dB SPL].
To compare the self-reported assessments of hearing outcome between the Investigational device and and the unaided situation.	At 3 and 6 months compared to preoperative. • Abbreviated Profile of Hearing Aid Benefit (APHAB). • Speech, Spatial and Qualities of Hearing Scale (SSQ).
To compare health-related quality of life (HRQoL) between the Investigational device and the preoperative hearing situation.	At 3 and 6 months compared to preoperative. • Health Utilities Index (HUI).
To collect surgical information.	• Soft tissue thickness (mm) • Type of anesthesia (general/local) • Bone polishing/removal at the actuator site (yes/no) • BI300 Implant length (3mm/4mm) • Location of BI300 Implant (mm between the ear canal and the center of the actuator). • Soft tissue reduction (yes/no) • Surgical incision type (examples; C-shaped/S-shaped/straight) • Location of the surgical incision in relation to the actuator (anterior/posterior) • Estimated length of the surgical incision (mm) • Placement of the coil (periosteal pocket (under periosteum)/on top of periosteum/on top of muscle) • Surgery time (time between first incision to last suture)
To collect information about the usability.	• Magnet choice • Sound Processor retention • Sound processor wearing comfort • Use of SoftWear pad • Daily use • Daily streaming time • Battery lifetime

To compare hearing performance between the Investigational device and a Baha 5 Power Sound Processor on a Baha Softband (preoperative).	At fitting, 3 and 6 months compared to preoperative. • Thresholds audiometry, free-field [PTA4, Mean of 0.5, 1, 2 and 4 kHz]. • Thresholds audiometry, free-field [0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0 and 8.0 kHz]. • Adaptive speech in noise [signal-to-noise ratio, 50% speech understanding]. • Speech in quiet [% correctly perceived words at 50dB, 65dB and 80dB SPL]. • BC Direct [0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0 and 6.0 kHz].
Safety Objective	**Safety Outcome measures**
Primary safety analysis 3 months post-surgery	
Implant site evaluation	Numbness will be collected from Suture removal and onwards.
Adverse events	Information will be collected from Surgery and onwards.
Device deficiency	Information will be collected from Surgery and onwards.
Concomitant medication	Information will be collected from Surgery and onwards.

6.3 Tertiary Objective

Tertiary Objectives	Outcome measures
To measure hearing performance preoperatively with a current hearing aid (if used by the patient).	• Adaptive speech in noise [signal-to-noise ratio, 50% speech understanding].
To perform feedback measurements for the Investigational device	• Feedback measurements data

6.4 Exploratory Objective

Not applicable

7 DESIGN OF THE CLINICAL INVESTIGATION STUDY

7.1 General

This is a prospective, multicentre, open-label, single-arm, within subject comparison clinical investigation.

The subjects include men and women aged 18 years or older with a CHL, MHL or SSD. Subjects will be screened, and 30 eligible subjects will be included in the clinical investigation. Subjects who drop out prior to surgery will be replaced, in order to reach a total of 30 evaluable (implanted) subjects.

After surgical implantation of the device, subjects will attend scheduled study visits over a six-month study period to be assessed as described in the CIP Schedule of Events (Section 3). At study visits, subjects will be evaluated through objective audiological hearing tests, patient reported outcomes and safety assessments. The primary outcome is to determine the hearing performance of the Investigational device compared to unaided hearing, assessed by free field thresholds audiometry, [PTA4, Mean of 0.5, 1, 2 and 4 kHz] and Adaptive speech recognition in noise at 3 months post-surgery. Safety will be assessed by recording and summarising all AEs/ADEs and DDs.

7.1.1 Design Rationale

This clinical investigation is designed to collect data regarding the objective and subjective hearing performance and quality of life for the Investigational device. Safety parameters will also be collected. This investigation is limited to adult subjects, although the device is intended for both peadiatric and adult patients. The peadiatric population constitutes a heterogeneous patient group (age-related), and there are currently no audiological tests suitable for comparisons across age ranges and across multiple countries/languages. Subjects with either CHL or MHL (≤ 55 dB SNHL) or SSD are included, since these are the intended patient populations for the Investigational device.

The investigation will be performed in an open design since it is not possible to perform the investigation in a blinded fashion.

The main evaluations of the investigation, i.e. audiometric thresholds (pure tone average PTA4) and speech recognition in noise measured in free-field, are relevant and objective methods that are commonly used by clinics internationally as a way to assess hearing performance.

Threshold audiometry is not language specific (no words used), thus rendering comparative data in an international, multilingual setting.

Speech communication is a very important aspect in human communication. In everyday life, conversations usually occur in the presence of background noise and listeners with hearing-impairment often complain about problems with understanding speech in noisy situations. Speech in noise tests resemble everyday situations (listening to complete sentences in noise) and can therefore be used to test the performance of hearing in noisy situations. The Hearing in Noise Test (HINT) is a speech in noise test designed to be used in an adaptive procedure to establish the speech recognition threshold for sentences, where 50% of the sentences are correctly repeated. The original HINT material was developed in 1994 and consists of short everyday sentences in English, which are judged to be natural by native speakers of American English (10). The Chinese Hearing in Noise Test (CHINT) was developed using the same rationale as the English HINT and have shown to be comparable, allowing the two tests to be compared directly across languages (11). In Australia an adaptive Australian Sentence Test in

Noise, the AuSTIN test will be used, which is validated in terms of test-retest reliability and efficiency (12).Questionnaires to collect patient reported outcomes—Abbreviated Profile of Hearing Aid Benefit (APHAB) (13) and Speech, Spatial and Qualities of Hearing Scale (SSQ) (14) and the health related quality questionnaire, HUI (15) are well established methods that are abundantly referred to in the scientific literature.

The Baha 5 Power Sound Processor on a Softband was chosen as a secondary assessment. The Baha 5 Power Sound processor has the same fitting range (55 dB SNHL) and intended target population as the Investigational device. When used on a Softband, the Baha 5 Power Sound Processor is a relevant choice to present as a pre-operative listening for the subject, thus offering the patient the possibility to experience bone conducted sound prior to implantation.

The follow-up period of 3 months post-surgery for the primary analysis is chosen as it is judged as long enough for the subjects to adapt and get used to the hearing performance with the Investigational device. The total length of the investigation is judged to be adequate for evaluating safety, as most safety issues are likely to be related to general risks associated the surgical intervention and thus occur early in the study. Six months data from a clinical study with a predecessor device of the Investigational device confirmed that the device is effective and safe.

In summary, this investigation is expected to demonstrate that the Investigational device performs within its intended use and is a suitable treatment for adult patients with a CHL, MHL or SSD.

7.2 Subjects

Signed informed consent must be obtained from the subject before any study procedures are initiated.

Eligibility of enrolled subjects must be supported by unaided audiometric threshold measures (including both air- and bone conduction thresholds) at screening to demonstrate that the subject meets the audiological inclusion criteria.

Bilateral surgeries are allowed. However, performance data for the Investigational device will only be collected for one of the ears, as judged by the investigator as the “test ear”.

7.2.1 Inclusion Criteria

Subjects must meet all of the inclusion criteria described below to be eligible for this clinical investigation.

1. Subject with CHL or MHL in the ear to be implanted. Bone conduction thresholds with pure tone average (PTA4; mean of 0.5, 1, 2 and 4 kHz) of ≤ 55 dB SNHL.

   OR

   Subject with SSD who is a candidate for Baha surgery. Air conduction thresholds with a pure tone average PTA4 (mean of 0.5, 1, 2 and 3 kHz) of ≤ 20 dB SNHL in the good ear OR subject who is indicated for an AC CROS but—for some reason—cannot or will not use an AC CROS (Air Conduction-Contralateral Routing of Signal).

2. Adult subjects (18 years or older).
3. Previous experience from amplified sound through properly fitted amplification (for example but not limited to Hearing aid, CROS device, Bone conductional hearing device on softband).
4. Candidate is a fluent speaker in the language used to assess speech perception performance
5. Willing and able to provide written informed consent.

7.2.2 Exclusion Criteria

Subjects who meet any of the exclusion criteria described below will not be eligible for this clinical investigation.

1. Uncontrolled diabetes as judged by the investigator.
2. Condition that could jeopardise osseointegration and/or wound healing (e.g. osteoporosis, psoriasis, long-term systemic use of corticosteroids) or condition that may have an impact on the outcome of the investigation as judged by the investigator.
3. Insufficient bone quality and quantity to support successful implant placement.
4. Previous surgery and/or implantation with any bone conduction/active device on the side to be implanted, which jeopardize the implantation and use of the Osia 2 system, as judged by the investigator.
5. Use of ototoxic drugs that could be harmful to the hearing, as judged by the investigator.
6. Unable to follow investigational procedures, e.g. to complete quality of life scales, or unwilling to comply with the requirements of the clinical study as determined by the Investigator.
7. Condition with a likely negative progression and/or with expected relapses jeopardising general wellbeing and health-related quality of life as judged by the investigator.
8. Subject that has received radiotherapy in the area of implantation or is planned for such radiotherapy during the study period.
9. Investigator site personnel directly affiliated with this study and/or their immediate families; immediate family is defined as a spouse, parent, child, or sibling.
10. Cochlear employees or employees of Contract Research Organisations or contractors engaged by Cochlear for the purposes of this investigation.
11. Currently participating, or participated within the last 30 days, in another interventional clinical investigation involving an investigational drug or device.

7.2.3 Number of Subjects Required

Thirty subjects are to be enrolled in the investigation, i.e. will receive the implant.

It is expected that approximately 33 subjects are to be screened to meet this sample size.

7.2.4 Vulnerable Populations

Not applicable.

7.2.5 Enrolment & Investigation Duration

The following subject status definitions apply:

Screened: A consented subject who is being assessed for eligibility according to the Screening requirements.

Screen Fail: A consented subject that has been determined to not meet all eligibility criteria for enrolment.

Enrolled: Subjects who have met all eligibility criteria and have received the implant.

If a subject discontinues his/her participation in the investigation, he/she will not be replaced if this discontinuation occurs after surgery is performed. If this discontinuation occurs before surgery the subject will be replaced in order to reach 30 evaluable subjects.

The enrolment period for the investigation is anticipated to be approximately 4 - 6 months from the time of first subject consent to enrolment of the last subject.

The expected duration of each subject's participation in the investigation, is 6 months from surgery.

The anticipated total duration of the clinical investigation is maximum 12 - 15 months.

Completion of investigation is defined as last subject last visit. In the event of an ongoing SADEs at the time of this last visit, the investigation completion will be extended for a further 30 days, or until resolution or stabilisation of the event, whichever comes first.

7.2.6 Criteria for Subject Withdrawal

Subjects can decide to withdraw from the investigation at any time. The investigator shall ask for the reason(s). The reason for withdrawal should to be documented in the subject's source files and the CRF.

The investigator or Sponsor may also decide to withdraw a subject from the clinical study if it is considered to be in their best interests.

Subject withdrawal may be for any of the following reasons:

- Adverse Event (AE)
- Device Deficiency (DD)
- Repeated and severe CIP or GCP deviation
- Subject lost to follow-up
- Subject withdrew consent

- Subject death
- Sponsor decision
- Investigator decision
- Other (specify)

If subject withdrawal is due to problems related to the Investigational device, safety or performance, the investigator shall ask for the subject's permission to continue in safety follow up (i.e. adverse events) until their scheduled final study visit.

If a subject is lost to follow-up, every possible effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation. At least three separate attempts taken to contact the subject must be documented.

7.2.7 Randomisation Procedures

Not applicable.

7.2.7.1 Blinding Procedures

Not applicable.

7.2.8 Post-Investigational Medical Care

After the clinical study the subjects will be able to continue with their Investigational device. Routine controls with audiological checks will follow local routines according to the standard treatment program for bone conduction hearing implant systems. The Investigational device will be warranted and supported with service according to normal regional Cochlear routines.

7.3 Performance Evaluations and Procedures

7.3.1 Eligibility Evaluations and Procedures

Demographics

The following demographic data will be recorded at Screening and Baseline:

- Age collected as date of birth (month and year)
- Gender
- Race
- Nicotine use (Cigarettes/day)

Medical history

The following information will be recorded at Screening and Baseline:

- Relevant medical and surgical treatment during the past three years as judged by the investigator
- Current concomitant medication and treatments

Hearing history

During Screening and Baseline a number of baseline characteristics will be recorded:

- Type of hearing loss: (Conductive, Mixed or SSD)
- Aetiology of hearing loss: (chronic) infection, tumor, trauma, malformation, otosclerosis, other

Device history

- Current hearing aid (yes/no, specify model and brand, side and years of hearing aid use, reason for change)
- Previous experience from amplified sound through properly fitted amplification (specify type, duration of use, when stopped use, reasons stop using)
- Has the subject previously been suggested a bone conduction hearing implant solution? (yes/no, reason for rejection)
- Has the subject previously had a Baha implant (yes/no, reason for changing)

Treatment ear

Treatment ear (indicate left or right or both. In case of both, indicate “test ear”).

Audiogram

Unaided audiometric threshold measures (including both air- and bone conduction thresholds) should demonstrate whether the subject has a CHL, MHL or SSD and meets the audiological inclusion criteria.

An existing audiogram may be used as long as it has been completed during the last six months, and contains all the required relevant frequencies. Frequencies required for air conduction thresholds are 250, 500, 750, 1000, 1500, 2000, 3000, 4000, 6000 and 8000Hz. For bone conduction thresholds the required frequencies are 250, 500, 750, 1000, 1500, 2000, 3000, 4000 and 6000Hz. The subject’s pre-operative Pure Tone Average PTA4 for CHL and MHL (*mean of 500, 1000, 2000 and 4000Hz*) using unmasked BC thresholds and the Pure Tone Average PTA4 for SSD (*mean of 500, 1000, 2000 and 3000Hz*) using air conduction thresholds should be computed and measured in order to ensure that the subject meets the inclusion criteria.

If an audiogram is older than 6 months or does not contain the required frequencies, a new audiogram shall be performed at Screening/Baseline. Frequencies required for air conduction

thresholds are 250, 500, 750, 1000, 1500, 2000, 3000, 4000, 6000 and 8000Hz. For bone conduction thresholds the required frequencies are 250, 500, 750, 1000, 1500, 2000, 3000, 4000 and 6000Hz. Contralateral masking should be used if needed, and according to local practice. The site staff shall always measure both the unmasked thresholds, as well as and the masked thresholds if applicable.

Soft tissue thickness

At Screening and Baseline or at Surgery, depending on local practice and requirements, soft tissue thickness should be measured. The measurement should be performed in the centre of the marked coil position. For complete instruction and recommendation regarding the soft tissue thickness, see the Cochlear Osia OSI200 Implant Physicians Guide (9).

7.3.2 Post-Enrolment Evaluations and Procedures

7.3.2.1 Surgery

The Cochlear Osia OSI200 Implant Physicians Guide does not take into account any particular circumstances or factors relevant to an individual patient or case. Other surgical approaches and variations are practiced and may be more appropriate in certain patient cases. After considering all relevant circumstances, factors and information in each case, the appropriate surgical procedure is determined by the responsible investigator exercising independent medical judgement. Complete information is found in the Cochlear Osia OSI200 Implant Physicians Guide (9). However, the ideal position of the OSI200 Implant is with the actuator close to and in horizontal line with the ear canal without touching the pinna (Figure 5). The ideal angulation of the implant is around 0° for the coil and the actuator (Figure 5). Depending on the anatomy and medical history of the patient the placement may vary, and the maximal deviation should be 45° for the coil or actuator (Figure 6 A and B). The transmitting range of the OSI200 Implant is dependent of the soft tissue thickness; if the soft tissue thickness is exceeding the recommended thickness it will have a negative impact on the sound processor performance and magnet retention. Take patient hair and potential use of optional Cochlear SoftWear Pad into consideration when determining if soft tissue thinning is needed.

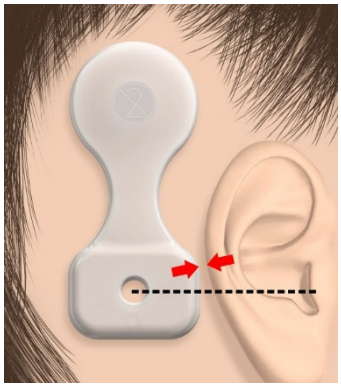

Figure 5: Ideal OSI200 Implant placement.

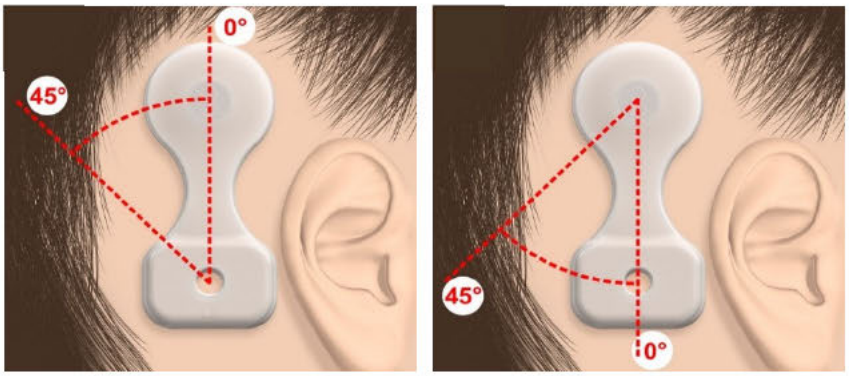

Figure 6: The maximum deviation should be 45° for either the coil (A) or the actuator (B).

During surgery the following variables should be collected:

- Soft tissue thickness (mm) (if not collected already at Baseline visit)
- Type of anesthesia (general/local)
- Bone polishing/removal at the actuator site (yes/no)
- BI300 Implant length (3mm/4mm)
- Location of BI300 Implant (mm between the ear canal and the center of the actuator).
- Soft tissue reduction (yes/no)
- Surgical incision type (examples; C-shaped/S-shaped/straight)
- Location of the surgical incision in relation to the actuator (anterior/posterior)
- Estimated length of the surgical incision (mm)
- Placement of the coil (periosteal pocket (under periosteal)/on top of periosteum/on top of muscle)
- Surgery time (time between first incision to last suture)

At approximately 2 weeks after surgery, sutures should be removed.

7.3.2.2 Audiometry testing

GENERAL INSTRUCTIONS FOR AUDIOLOGICAL ASSESMENTS

A detailed work instruction regarding the audiological assessments will be available during training before the start of the study.

Simultaneous bilateral implantation

In the case of a subject receiving simultaneous bilateral Investigational device, one of the treatment ears will be selected as the “test-ear”, tested for efficacy purposes. All tests will be

performed for the “test ear” alone and the other ear blocked. Selection of the “test ear” will be as judged by the responsible investigator prior to surgery. Patient-reported outcomes (APHAB, SSQ) and quality of life assessment (HUI), will be collected post-surgery in a bilateral hearing situation. Safety-related information, including adverse events and device deficiencies, will be collected and reported for each side receiving the Investigational device, i.e. for the whole subject.

Current hearing aid

If the subject is currently using a hearing aid at Screening/Baseline, the speech in noise test shall also be performed with the current hearing aid.

Blocking

All audiometric tests shall be performed with the non-test ear blocked (in case of normal or near-normal hearing or a large asymmetry with the non-test ear having significantly better hearing thresholds). Before blocking of the non-test ear a free-field measurement on PTA4 frequencies (500, 1000, 2000, 4000 Hz) shall be performed. The blocking shall then be done with earplug and muff and a additional free-field measurement on PTA4 frequencies shall then be performed to verify effective blockage and document the hearing level after blockage.

Settings for the Sound Processors

The Investigational device and the Baha 5 Power SP should be tested using the Everyday program.

AUDIOLOGICAL ASSESSMENTS

General set up

All tests shall be performed in a sound insulated room. Equipment used for audiological testing shall be calibrated before initiation of the study. The speakers should be at the height of the test subject’s head and more than 1 metre away from the test subject. There should preferably be more than 1 metre of free space around the test subject in all directions. This is in accordance with the current standard (16). It is important to keep the same sound room and test equipment set-up during the entire clinical study. ***Changes may be necessary and allowed, but only after approval by the Sponsor.***

Sound Processor fitting

The BFS of current market release will be used at Screening and Baseline when the fitting procedure should be performed for the Baha 5 Power Sound Processor on a Softband as a reference device.

The currently released version of OFS will be used to adjust the Investigational device settings for a specific subject. This will be performed during fitting, and throughout the study as needed (for example if the magnet is replaced with a different strength or start/stop of use of a soft pad). If the gain needs to be adjusted or changes to the program configuration are needed, a fine tuning is recommended. The fitting software will be installed on a laptop computer provided by the Sponsor, and the fitting-data will be saved on the laptop until the study is ended when it will be transferred to the Sponsor in a coded way.

Coil-to-coil measurement

The Digital Link Calibration (e.g. coil-to-coil measurement) that is a step in the connection step in the OFS, should be performed at each occasion the software is being used to fit or finetune the device to optimise the performance of the device for the user throughout the study. This will also provide an indication of the soft tissue thickness during the course of the study.

Feedback measurements

For the sound processor's Individual Stable Gain (e.g. feedback measurements as part of the FS) the feedback analyser test should be performed at each occasion the software is being used to fit or finetune the device to optimise the performance of the device for the user throughout the study. For the Investigational device this data will be collected, saved and eventually transferred to the Sponsor for analysis.

Bone Conduction (BC) Direct

BC Direct is a tool in the OFS and BFS (current versions) to establish the unmasked bone conduction threshold with tones presented through the sound processor. At Baseline, BC Direct data shall be collected with the Baha 5 Power SP on a Softband using the BFS and shall be used to calculate the fitting (settings) of the SP for the Softband test. BC Direct measurements (as part of the OFS) will also be performed from fitting to Follow up 6M when the subject is using the Investigational device. BC thresholds obtained at the following frequencies will be recorded; 250, 500, 750, 1000, 1500, 2000, 3000, 4000, 6000 Hz.

Free-field thresholds

The purpose of this test is to establish the hearing thresholds in free field through a speaker in front position (0 degrees azimuth) according to the so-called ascending or modified Hughson-Westlake method (Figure 7). The frequencies to be tested are [0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0 and 8.0 kHz], the signal to be used shall be warble tones.

At Baseline, free-field thresholds shall be measured for the unaided situation and with the Baha 5 Power Sound Processor on a Baha Softband.

At the fitting visit and at 3 and 6 months this test shall be performed with the Investigational device.

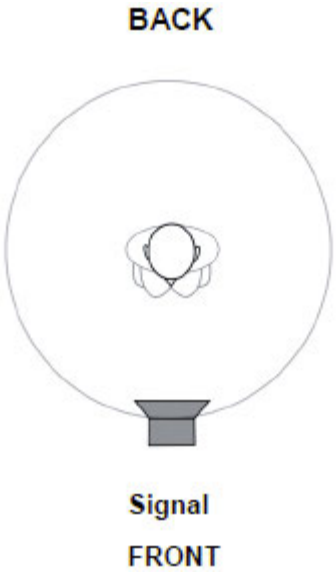

Figure 7: The setup of the speaker when testing Free-field thresholds and Speech recognition in quiet.

Speech tests

Speech recognition in quiet

The purpose of this test is to establish the test subject's ability to recognise speech in a quiet surrounding. The speech test in quiet shall be performed using phonetically balanced monosyllabic words presented in free field through a speaker from the front (0 degrees azimuth) (Figure 8). The test material shall be monosyllables and presented at 50-, 65- and 80-dB sound pressure level (SPL) and scores shall be recorded as % correctly repeated words at each presentation level. The length of the list shall be validated according to the language, preferably a 50 word list.

At Baseline the speech in quiet test shall be performed for the unaided situation and Baha 5 Power Sound Processor on a Baha Softband.

At the fitting visit and at 3 and 6 months this test shall be performed with the Investigational device.

Adaptive Speech recognition in noise

The purpose of this test is to establish the test subject's ability to recognize speech in the presence of background noise. The adaptive speech test in noise shall be conducted using validated lists for the language it is presented in. The first list shall be used as a training list before the test is performed and the training list shall be used at each visit. Both speech and noise will be presented in free field from the front speaker (0 degrees azimuth) (**Figure 8**). In Hong Kong software and speech material to be used is the CHINT (11), where the noise shall be kept constant at 65 dB SPL, and the speech shall be adapted stepwise according to the software used to establish the signal-to-noise ratio (SNR) where the test subject repeats 50% of the material correctly. In Melbourne and Sydney, the test to be used is AuSTIN (12). The sentences shall be presented at a constant level of 65 dB SPL throughout the test, and the

babble noise shall be adapted stepwise according to the software used to establish the speech-to-noise ratio (SNR) providing a 50% level of correctly repeated morphemes.

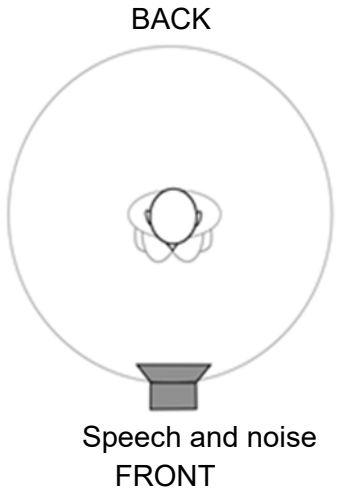

Figure 8. The setup of the speakers when testing Adaptive Speech recognition in noise.

At Baseline, the speech in noise test shall be performed for the unaided situation and Baha 5 Power sound processor on a Baha Softband. If the subject has a current hearing aid, the test shall also be performed with the hearing aid at Baseline. At the fitting visit and at 3 and 6 months this measurement shall be performed with the Investigational device.

7.3.2.3 Patient reported outcomes

Abbreviated Profile of Hearing Aid Benefit (APHAB form A)

The APHAB form “A” questionnaire (13) from HARL (Hearing Aid Research Lab, University of Memphis, USA) is a 24-item self-assessment inventory that evaluates the benefit experienced by the subject when using hearing amplification compared to the unaided listening. APHAB produces a global score and scores for four subscales: Ease of Communication, Reverberation, Background Noise, and Aversiveness.

The subjects will complete the APHAB questionnaire at Screening/Baseline, 3 and 6 months follow up.

- At Baseline, the subjects shall complete the questionnaire prior to the Softband test, and the questionnaire shall be answered with respect to the unaided hearing, even for subjects with a previous hearing device.
- At Follow up at 3 and 6 months, the subjects shall complete the questionnaire for the aided situation (with the Investigational device).

The APHAB questionnaire is available for free and in different languages on the HARL home page.

Speech, Spatial and Qualities of Hearing Scale (SSQ-12 version)

The short form of Speech, Spatial, and Qualities of Hearing Scale questionnaire (SSQ-12) (17) from MRC Institute of Hearing Research, UK, is a scaled-down version of the 49 items SSQ questionnaire (14). It is designed to compile a sub-set of items from the longer original 49 version to represent the scale as a whole, measuring self-reported auditory disability, reflecting the reality of hearing in the everyday world. It has been shown to provide similar results to SSQ49 (17). It covers:

- Hearing speech in a variety of competing contexts
- The directional, distance and movement components of spatial hearing
- Segregation of sounds and attending to simultaneous speech streams
- Ease of listening
- The naturalness, clarity and identifiability of different speakers, different musical pieces and instruments, and different everyday sounds

The subjects will complete the SSQ questionnaire at Screening/Baseline, 3 and 6 months follow up.

- At Baseline, the subjects shall complete the SSQ questionnaire prior to the Softband test and the SSQ questionnaire shall be answered with respect to an unaided hearing, even for subjects with a previous hearing device.
- At Follow up at 3 and 6 months, the subjects shall complete the questionnaire for the aided situation (with the Investigational device).

The SSQ-12 questionnaire was approved for use in this clinical study for free by Professor Michael Akeroyd, former Director of MRC Institute of Hearing Research, which closed down 2018.

Health Utilities Index (HUI)

HUI® (15) is a generic preference-based system for measuring comprehensive health status and health-related quality of life (HRQoL). HUI provides descriptive evidence on multiple dimensions of health status, a score for each dimension of health and an overall health-related quality of life (HRQoL). The scoring systems provide utility (preference) scores on a generic scale where dead = 0.00 and perfect health = 1.00. HUI3 will be used in this clinical study (Questionnaire HUI23S1EN.15Q). The HUI3 classification system is comprised of 8 attributes: Vision, Hearing, Speech, Ambulation, Dexterity, Emotion, Cognition and Pain – each with 5 or 6 levels of ability/disability (18). The version in this clinical study uses a recall time of 1 week.

The subjects will complete the HUI at Screening/Baseline, 3 and 6 months follow up.

- At Baseline, the subjects shall complete the HUI questionnaire prior to the Softband test and with respect to their current hearing situation.
- At Follow up at 3 and 6 months, the subjects shall complete the questionnaire for the aided situation (with the Investigational device).

The license to use the HUI questionnaire is purchased from Health Utilities Inc., 88 Sydenham Street, Dundas, ON, L9H 2V3 Canada.

7.3.2.4 Usability

Magnet choice

At fitting the most suitable magnet for the SP shall be selected, and the instruction for use are found in Osia 2 Sound Processor User Manual shall be followed. It is important that the strength is not too weak or too strong. There are 4 different strengths, ranging from 1 to 4, strength 1 being the weakest. During the follow up visits the choice of SP magnet shall be checked and recorded. There may be a need to decrease or increase the strength depending on the subject's preference. Every time a change occurs it is important to perform a new fitting procedure according to the OFS.

Sound Processor retention

At first fitting and all follow up visits, the subjects shall estimate the experienced retention of the SP.

The estimation shall be performed using the VAS scale (visual analogue scale 100mm) with insufficient retention to the left and excellent retention to the right.

With regard to your Sound processor, please rate the overall retention by placing a single vertical line on the scale.

Insufficent retention	*Excellent retention*

Sound Processor wearing comfort

At first fitting and all follow up visits, the subjects shall estimate the experienced wearing comfort of the SP.

The estimation shall be performed using the VAS scale (visual analogue scale 100mm) with no comfort at all to the left and excellent comfort to the right.

With regard to your Sound processor, please rate the overall comfort by placing a single vertical line on the scale.

Not comfortable at all	*Most comfortable imaginable*

Daily use

At all follow up visits data regarding daily use of the sound processor will be collected.

Average hours of daily use (hours/day) during the last week before each Follow up visit shall be recorded.

Daily streaming

At all follow up visits, data regarding daily streaming using the sound processor shall be collected.

Average hours of daily streaming (hours/day) during the last week before follow up shall be recorded.

Battery lifetime

During the clinical investigation SP battery lifetime will be followed from 6 weeks post surgery. At the follow up visit, data regarding battery lifetime for the sound processor will be collected. Average hours of the battery lifetime for a single battery during the last week before each follow up visit. Subjects will be encouraged to use each battery until the “low battery” is signaled by the SP.

SoftWear Pad use

During the clinical study at first fitting and at each follow up visit, data regarding SoftWear pad use (Yes/No) for the sound processor will be collected.

7.3.2.5 Device exposure

Device exposure is information about for how long the subject is exposed to the Osia 2 Implant and the Osia 2 Sound Processor. Data is summarized from other data fields in the same case report form.

7.4 Safety Evaluations and Procedures

Subjects will be carefully monitored during the study for possible adverse events and appropriate treatment of the subject will be initiated. Any adverse events observed will be fully investigated by the investigator and documented in the CRF including assessment of seriousness, severity (mild, moderate or severe) and relationship to the medical device.The risks and anticipated ADEs for Osia 2 System, as identified in Section 8.3 of the CIP, will be assessed in the clinical study via reporting of all AEs/ADEs from the time of first subject first visit until last subject last visit. The Sponsor will be notified by automatic eCRF alerts when

events are judged as device related or serious. A safety monitor, appointed by the Sponsor, will be contacted regarding events that are uncertain, serious or unexpected.

7.4.1 Numbness

At all visits from Suture removal the subjects will be assessed for any presence of numbness over and around the implant area at Suture removal and throughout the study. The following scale will be used:

1. No numbness

2. Numbness over the implant Magnet Assembly area (inside red circle in Figure 9).

3. Numbness over the implant Magnet Assembly area (inside red circle in Figure 9) and 2 cm beyond the implant.

Numbness will be assessed by means of a pin and a cotton swab. Randomly picked locations over the implant Magnet Assembly area and from the edge of the implant and 2 cm out (beyond the implant) will be tested by gently touching the skin with the pin and the cotton swab. No sampling on the incision line or above the surface of the actuator.

The scale above shall be used to score the subject's sensation to stimulus with the pin and with the cotton swab.

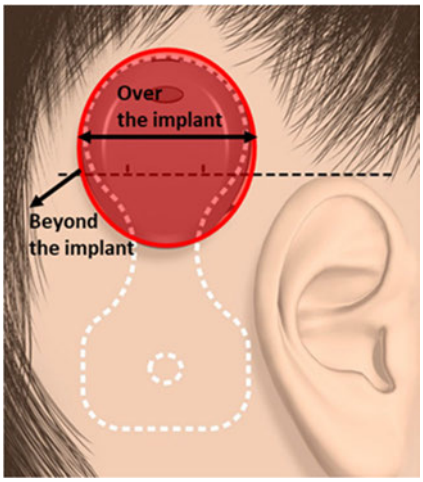

Figure 9: Numbness will be measured over the implant Magnet Assembly area or over and beyond the implant Magnet Assembly area.

7.4.2 Concomitant Medication and Therapies

All medications and treatments given, whether or not to treat AEs/ADEs, must be recorded in the appropriate section of the CRF.

Prohibited therapies are the following:

- long-term systemic use of corticosteroids

- ototoxic drugs
- radiotherapy in the area of implantation

If a subject receives a prohibited therapy each situation will be evaluated case by case and judged by the responsible investigator.

7.5 Equipment Used for Evaluation of Performance and Safety

All tests shall be performed in a sound insulated room. Equipment used for audiological testing shall be calibrated in accordance the local procedures at each clinic. A work instruction will be provided by the time of the Site Initiation Visit.

A laptop with OFS together with a user manual for the software according to current released version and a HiPro box will be provided by the sponsor.

7.6 Sponsor Role in Conduct of the Clinical investigation

The test set-up regarding speaker placement, sound room facility and software used at each clinic shall be checked and approved by the Sponsor at the latest during the Site initiation visit. Equipment used for audiological testing shall be calibrated before initiation of the study. Calibration certificates will be asked for by the Sponsor as part of the study documentation.

The sponsor will have a representative as support during the first surgery (or surgeries) as well as during first audiological testings and/or fitting.

8 RISKS AND BENEFITS OF THE INVESTIGATIONAL DEVICE AND CLINICAL INVESTIGATION

8.1 Anticipated Clinical Benefits

The Investigational device is an active implantable BCHIs combining the distinct advantages of the percutaneous and transcutaneous Baha systems. A recipient is expected to experience the following clinical benefits when using the system:

Efficient sound transmission through direct bone conduction, without the inherent medical and cosmetic drawbacks of a percutaneous (skin-penetrating) abutment.

Compared to passive transcutaneous BCHIs (e.g. the Baha Attract System), the Investigational device provides a more efficient transmission of sound, especially in the high frequency range, as the actuator (vibrator) is directly coupled to the bone, eliminating the attenuation of vibrations through the soft tissue that is inherent to the passive system. With the Investigational device it is also possible to position the transducer closer to the ear canal, which may further improve audiological outcomes. The Investigational device is designed to provide hearing benefit to patients with conductive, mixed or sensorineural hearing loss of up to 55 dB,

similar to a Power SP (e.g. Baha 5 Power) on abutment. Skin complications requiring treatment and/or precluding the use of the sound processor are relatively frequent for percutaneous devices (e.g. the Baha Connect System) due to the exposed abutment. For percutaneous abutments, daily site care is required to maintain a reaction-free skin penetration, but is not a guarantee for successful outcomes. For this transcutaneous Investigational device, the implant site is sealed and does not provide a direct path for infections. In addition, a transcutaneous system, without an abutment protruding through the skin, is often perceived as a more aesthetic option.

State-of-the-Art signal processing and wireless connectivity

The Investigational device is built around the same platform for audio signal processing and wireless functions as the Baha 5 family of Sound Processors with Bluetooth® Smart technology, made for iPhone (MFi) with support for direct audio and data streaming, and 2.4 GHz wireless technology that connects to Cochlear Wireless Accessories (e.g. MiniMic 2 and 2+, Phone clip, TV streamer, Remote control 2).

In addition to the overall clinical benefits provided by the Investigational device, participation in this clinical study is anticipated to benefit the subject by providing early, pre-market access to the latest technology within BCHI Systems.

8.2 Anticipated Adverse Device Effects

The Investigational device has been designed and manufactured to ensure that all risks have been reduced as far as possible. However, certain adverse device effects (ADEs) may occur even after all state-of-the-art risk control measures have been implemented and verified.

As per section 4.2.2, safety and performance of the Osia System (predecessor device) has been tested in a prospective, multicentre clinical study. The following adverse device effects have been reported (to date) and may be relevant to the participants of this clinical study (more detail provided in the IB):

- One (1) serious adverse event (SAE) has been reported for the Osia System involving the removal of an Osia Implant due to a wound infection starting shortly after surgery: *possibly related to the procedure (reported by investigator).*
- Forty one precent (41%) of system related adverse events (n=28) were related to the surgical procedure. These adverse events were mostly mild and transient (e.g. post-operative pain, swelling or irritation). The device-related adverse events (n=11 were reported as warmth from SP (n=2), headache (n=1), position vertigo (n=1), feeling of tension at implant site (n=1), pain (1), numbness (n=1) and change in bone conduction thresholds (3).

More information and details with regards to any risks with the use of the Investigational device is provided in the Investigator´s Brochure.

8.3 Risks Associated with Participation in the Clinical investigation

Subjects participating in the clinical study are exposed to the anticipated adverse device, and or procedure related effects associated with standard Baha and Osia implant surgery and in connection with general anaesthesia.

The following potential complications and adverse effects are stated in the OSI200 Implant Physician's guide (9).

Prospective implant recipients should be advised of the following risks:

- General risks associated with surgery and general anaesthesia.
- Osseointegration failure – potential causes for failure of osseointegration include lack of adequate bone quantity/quality, trauma, infection, generalised diseases and surgical complications.
- Other medical complications that may require additional medical treatment, such as:
    - Concurrent Cerebrospinal Fluid (CSF) leakage
    - Subdural injury
    - Subcutaneous haematoma
    - Irritation, inflammation or breakdown of the skin flap; infection; and in some cases, extrusion of the device caused by the presence of a foreign body under the skin

Failure of device component parts (both external and internal) could result in the perception of an uncomfortably loud sound sensation, intermittent sound, or no sound.

Partial or full failure of the device could require removal or replacement of the implant.

While the majority of risks are associated with the surgery it cannot be excluded that soft tissue related complications may occur.

Investigators and users shall be aware of the following:

- If the user experience tightness, numbness or even pain at the implant site, or develop significant skin irritation, he/she shall stop using the sound processor and contact the investigator.
- Signs of overheating and signs of discomfort or skin irritation at the implant site.
- Occasional feedback and/or noise may occur.

8.4 Risk Mitigation

The Osia 2 System has been designed and manufactured to ensure that all risks have been reduced as far as possible; however, as with any surgical intervention, a 100% success rate cannot be guaranteed. As such, the following will be performed during the clinical study to further mitigate the risks identified above:

- Before start of each site in the clinical study each investigator will have done documented surgery training according to the Cochlear Osia OSI200 Implant Physician's Guide either at a cadaver lab or on a plastic skull.
- The suggested surgical approach and the two new tools have been validated by 27 surgeons in 4 regions and will be described in a usability report under preparation by the time of this final CIP *(6)*.
- CBAS qualified staff will be present during one or more of the first surgeries at each clinic in order to support any surgical questions or issues related to the OSI200 Implant.
- All reported ADEs and DDs will be reviewed regularly by the Sponsor for the duration of the study to facilitate early detection and appropriate intervention if events are unanticipated with respect to incidence, severity, or outcome.
- MRI examinations can be performed safely on a person with this implanted device only under very specific conditions. An MRI information package is supplied with each implant for additional information regarding magnetic resonance imaging (19). Subjects enrolled in the study that receive the Osia 2 System will receive an MRI card, for information to radiologists if an evaluation and planning of any MRI examination becomes necessary. Subjects that have received radiation therapy, or are planned for radiation therapy during the study, at the same side of the skull where the Osia 2 System will be positioned are excluded from the study.
- Users shall routinely check the device for signs of overheating and for signs of discomfort or skin irritation at the implant site and inform the study staff.
- Do not apply continued pressure to the processor when in contact with the skin (e.g. sleeping while lying on processor, or using tight fitting headwear).

8.5 Risk-to-Benefit Rationale

The Investigational device has been designed to make the implant more robust, reduce complexity of the surgery and provide a more advance sound processor compared to the precursor Osia System. The predecessor system has been shown to be safe and effective in a multicentre clinical investigation.

As with the predecessor device, most of the risks identified for the Investigational device are related to surgery and/or implant failures leading to explantation (further details are provided in the Investigator´s Brochure).

The design modifications to the Investigational device compared to the predecessor implant (OSI100), as described above, have resulted in a more robust implant thought to reduce the occurrence rate / likelihood of implant failures leading to explantation. In addition, the shorter and less complex surgical procedure required for Investigational device implantation is believed to mitigate the general risks associated with surgery and general anaesthesia.

Based on the data presented herein, the relatively low risk associated with the intended use of the device, and the added benefit to the patient, it is believed that the anticipated risks related

to the intended use of the Investigational device are well within the acceptable limits when weighed against the benefits to the patient.

9 STATISTICAL CONSIDERATIONS

9.1 General Considerations

The distribution of continuous variables as well as change in continuous variables will be given as n, mean, SD, SEM, Median, Min and Max and the distribution of dichotomous and categorical variables will be given as number and percentages. For continuous variables estimated mean and the 95% two-sided confidence interval (bootstrapped) for difference between groups will be presented.

Since all included subjects will have measurements of the primary and important secondary efficacy variables for unaided hearing, with the Investigational device and with a Baha Power sound processor on a Baha Softband, all statistical analyses will be paired. All statistical analyses will be non-parametric. In order to choose the most powerful test, the Fisher's non-parametric permutation test for paired observations will be used for all paired analyses of continuous variables. The permutation tests use the measured values and not only the ranks in the calculations. For paired analysis of dichotomous and ordered categorical variables the Sign test will be used.

The main efficacy analyses will be performed at 3 months after surgery on the ITT population and complementary efficacy analyses will be performed 6 months after surgery on the ITT population. In addition, all analyses will be made on the PP population. Sub analyses will also be performed on one group consisting of Mixed/conductive subjects and one consisting of SSD subjects.

Imputation of missing values will be performed for all efficacy variables using stochastic regression imputations. All ITT analyses will be performed/presented both for the imputed and for the non-imputed data (sensitivity analyses).

The final definition of the analysis sets (ITT, PP and Safety) will be taken at the clean file meeting before database lock. See separate paragraph for definitions.

A statistical analysis plan (SAP) with detailed statistical analyses specified for all variables and time points will be written and signed before the database lock.

The approximate number of subjects per site is 10 and the maximum is approximately 15. See separate paragraph for Sample size calculation.

Major protocol deviations are those that are considered to have an effect on the analysis. The number of patients with major protocol deviations will be summarised per treatment group. A list of protocol deviations will be produced.

Imputation of missing values will be performed for all efficacy variables. No imputation of baseline values or baseline carry forward will be made. Imputations will be made according to the following rules:

1. If a value is missing at the end of a patient, last observation will be carried forward.
2. If a missing value is occurring between two time points with values, an interpolation will be made for continuous variables and for categorical variables the value from the previous visit will be carried forward.

The number of patients with major protocol deviations will be summarised per treatment group. A list of all protocol deviations will be produced.

9.2 Outcome measures

9.2.1 Primary Outcome measures

The improvement in hearing performance when using the Investigational device at 3 months post-surgery compared to the preoperative unaided situation assessed as:

- Thresholds audiometry, free-field [PTA4, mean of 0.5, 1, 2 and 4 kHz].
- Adaptive speech in noise [speech-to-noise ratio, 50% speech understanding].

9.2.2 Secondary Outcome measures

- The improvement in hearing performance at fitting and 6 months post-surgery when using the Investigational device compared to the unaided situation assessed as:
  - The improvement in Thresholds audiometry, free-field [PTA4, mean of 0.5, 1, 2 and 4 kHz]
  - The improvement in Adaptive speech in noise [signal-to-noise ratio, 50% speech understanding].
- The improvement in hearing performance at fitting, 3- and 6 months post-surgery when using the Investigational device compared to the unaided situation assessed as:
  - The improvement in Thresholds audiometry, free-field [0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0 and 8.0 kHz].
  - The improvement in Speech in quiet [% correctly perceived words at 50dB, 65dB and 80dB SPL].
- The benefit in self-reported hearing outcome when using the Investigational device at 3- and 6-months post-surgery compared to the unaided hearing assessed by:
  - The improvement in scores using the Abbreviated Profile of Hearing Aid Benefit (APHAB).
  - The improvement in scores using the Speech, Spatial and Qualities of Hearing Scale (SSQ).

- The benefit in health-related quality of life (HRQoL) measured by the difference in scores with HUI when using the at 3 and 6-months post-surgery compared to the pre-operative hearing situation.
- Surgical information:
    - Soft tissue thickness
    - Surgery time
    - Bone polishing/removal at the actuator site
    - BI300 Implant length
    - Location of BI300 Implant
    - Type of anaesthesia
    - Soft tissue reduction
    - Surgical incision type
    - Length of the surgical incision
    - Placement of the coil
    - Location of the surgical incision in relation to the actuator
- Usage information:
    - Magnet choice
    - Sound Processor retention
    - Sound Processor wearing comfort
    - Use of SoftWear pad
    - Daily use
    - Daily streaming
    - Battery lifetime
- The difference in hearing performance between the Investigational device and to a Baha 5 Power Sound Processor on a Baha Softband (preoperative) assessed at fitting, 3- and 6-months post-surgery as:
    - The difference in Thresholds audiometry, free-field [PTA4, mean of 0.5, 1, 2 and 4 kHz].
    - The difference in Thresholds audiometry, free-field [0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0 and 8.0 kHz].
    - The difference in Adaptive speech in noise [signal-to-noise ratio, 50% speech understanding].
    - The difference in Speech in quiet [% correctly repeated words at 50dB, 65dB and 80dB SPL].
- BC Direct [0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0 and 6.0 kHz] will be performed using a Baha Softband (preoperatively) at screening/baseline and using the Investigational device at fitting, 3- and 6-months post-surgery.

9.2.3 Tertiary Outcome measures

- The difference in hearing performance at fitting- 3- and 6 months post-surgery when using the Investigational device compared to a preoperative hearing aid (if used by the patient) assessed as:
    - The difference in Adaptive speech in noise [signal-to-noise ratio, 50% speech understanding].
- Feedback measurements to be collected the Investigational device.

9.2.4 Exploratory Outcome measures.

There are no exploratory Outcome measures.

9.3 Hypotheses

The hierarchical testing procedure below is introduced to guarantee that the probability of Type I error is < 2.5% for all confirmative statements. The order of the hierarchical testing procedure will be:

1. PTA 4 pre-operative unaided vs. 3 months post-surgery (Primary efficacy analysis)
2. Adaptive speech recognition in noise (50% performance), signal to noise ratio (SNR) pre-operative unaided vs. 3 months post-surgery
3. Speech in quiet at 65dB SPL pre-operative unaided vs. 3 months post-surgery
4. APHAB Global pre-operative unaided vs. 2 months post fitting aided
5. Hearing attribute (HUI) pre-operative situation vs. 3 months post-surgery
6. Mean of the 12 items (Total score) in the SSQ pre-op unaided vs. 3 months post-surgery

If the first analysis is significant the probability mass 0.025 will go to the second analysis. If the second analysis is also significant the probability mass 0.025 will go to the third analysis and so on. When the first non-significant analysis is reached this and all analyses thereafter will be non-confirmative while the previous analyses will be confirmative. If the first analysis is non-significant no analysis will be confirmative. All testing will be Alpha level of 0.025 and one sided test will be used and the analysis will be performed on the ITT.

9.3.1 Primary Hypothesis

Group mean free-field PTA4 (average of 500, 1000, 2000, and 4000 Hz) with the Investigational device at the 3-month postoperative interval will be improved over that measured preoperatively in the unaided condition (baseline).

This endpoint is represented by the following hypotheses:

$$\mathrm{H}_0\colon \mu_F - \alpha_0 = 0,$$

$$\mathrm{H}_\mathrm{a}\colon \mu_F - \alpha_0 \neq 0,$$

where:

α_0 = baseline preoperative PTA4;

μ_F = mean follow-up PTA4 3 months postoperative.

Alpha level of 0.05 and two sided test will be used and the analysis will be performed on the ITT population.

Group mean Adaptive speech recognition in noise (50% performance), speech to noise ratio (SNR) with the Investigational device at the 3-month postoperative interval will be improved over that measured preoperatively in the unaided condition.

This endpoint is represented by the following hypotheses:

$$\mathrm{H}_0: \mu_F - \alpha_0 = 0,$$

$$\mathrm{H}_\mathrm{a}: \mu_F - \alpha_0 \neq 0,$$

where:

α_0 = baseline preoperative Adaptive speech recognition in noise (50% performance), speech to noise ratio (SNR);

μ_F = mean follow-up Adaptive speech recognition in noise (50% performance), speech to noise ratio (SNR) 3 months postoperative.

Alpha level of 0.05 and two sided test will be used and the analysis will be performed on the ITT population.

9.3.2 Secondary Hypothesis

Group mean Speech in quiet at 65dB when using the Investigational device at 3 months postoperative compared to the unaided hearing.

This endpoint is represented by the following hypotheses:

$$\mathrm{H}_0: \mu_F - \alpha_0 = 0,$$

$$\mathrm{H}_\mathrm{a}: \mu_F - \alpha_0 \neq 0,$$

where:

α_0 = baseline preoperative word recognition score;

μ_F = mean follow-up word recognition score 3 months postoperative.

Group mean Global score using the Abbreviated Profile of Hearing Aid Benefit (APHAB) when using the Investigational device at 3 months post surgery compared to unaided hearing.

This endpoint is represented by the following hypotheses:

$$\mathrm{H}_0: \mu_F - \alpha_0 = 0,$$

$$\mathrm{H}_a: \mu_F - \alpha_0 \neq 0,$$

where:

α_0 = baseline APHAB Global score;

μ_F = mean follow-up APHAB Global score 3 months postoperative.

Group mean Hearing attribute (HUI) when using the Investigational device at 3 months post surgery compared to the preoperative hearing situation.

This endpoint is represented by the following hypotheses:

$$\mathrm{H}_0: \mu_F - \alpha_0 = 0,$$

$$\mathrm{H}_a: \mu_F - \alpha_0 \neq 0,$$

where:

α_0 = baseline Hearing attribute (HUI);

μ_F = mean follow-up Hearing attribute (HUI) 3 months post-fitting.

Group mean Total score using the Speech, Spatial and Qualities of Hearing Scale (SSQ) when using the Investigational device at 3 months post surgery compared to the unaided hearing.

This endpoint is represented by the following hypotheses:

$$\mathrm{H}_0: \mu_F - \alpha_0 = 0,$$

$$\mathrm{H}_a: \mu_F - \alpha_0 \neq 0,$$

where:

α_0 = baseline SSQ Total score;

μ_F = mean follow-up SSQ Total score 2 months post-fitting.

All other secondary outcomes will not be formally hypothesis tested but summarized and p-values will be calculated as described in 9.1 General considerations.

9.3.3 Exploratory Hypothesis

There are no exploratory hypotheses.

9.4 Sample Size Determination

Based on 6 months safety data from 51 subjects implanted with the predecessor Osia System at 5 clinics in the multicentre clinical investigation described in section 4.2.2.1 (8) it is judged that approximately 10 subjects per clinic and 3 clinics is reasonable for detecting any safety issues with the Investigational device in this study. The primary safety evaluation will be performed 3 months post-surgery, which with an estimation of 30 subjects will equate 7.5 patient years. This is considered to be enough safety data for the primary safety analysis.

With a total of 30 subjects, there will be a very high power to detect significant changes in the primary performance evaluations *audiometric thresholds (PTA4)* and *adaptive speech in noise (speech to noise ratio, SNR)*.

PTA4: Assuming the same mean reduction in PTA4 as in the multicentre clinical investigation of the predecessor Osia System (Mean change -25 dB, SD 9.5 dB), the resulting power with 30 subjects is 0.99.

SNR: In the multicentre clinical investigation of the predecessor Osia System a change in SNR from 4.98 dB (SD 7.76 dB) unaided to -8.19 dB (SD 6.58 dB) aided resulted in a mean improvement in SNR of -13.3 dB (SD 8.1 dB). In that investigation, speech was presented from the front and noise from the rear speaker. In the present investigation, however, both speech and noise will be presented from the front speaker, which is known to result in higher SNR values in the aided situation (the SNR in the unaided situation is not expected to change significantly). In a pilot clinical investigation conducted at Cochlear's own research facility (CBAS5271, Sub study 118), a mean SNR value of -2.5 dB was recorded with the Investigational device (Osia 2 System). Assuming that in the present investigation the unaided mean SNR is similar to the unaided scores in the multicenter investigation and that the aided mean SNR is similar to the pilot investigation, a mean improvement in SNR of approximately -7.6 dB (SD 8.1 dB) is expected. With 30 subjects, the resulting power is 0.99.

9.5 Analysis Populations

The final definition of the analysis sets (ITT, PP and Safety) will be taken at the clean file meeting before database lock.

- The Intention-to-Treat population (ITT) will include all subjects who have undergone surgical intervention.
- The Per Protocol population (PP) will include subjects that have completed the study according to the protocol. Subjects that were incorrectly included or were considered major protocol violators that affect the primary analysis should be removed from the PP population.
- The Safety population consists of all surgically treated subjects

All efficacy analyses will be performed on both ITT and PP populations.

9.6 Primary Outcome Analyses

Primary efficacy analysis will be determined by analysis of change in free-field threshold audiometry: PTA4 (mean of 500, 1000, 2000 and 4000Hz) and change in Adaptive speech recognition in noise (50% performance), from unaided versus Investigational device at 3 months post-surgery visit for the ITT population, using Fisher's two-sided non-parametric permutation test for paired observations at a significance level of 0.05 to demonstrate an improvement in PTA4. Both PTA4 and SNR must be significant at alpha 0.05 for the primary analysis to be considered as confirmative.

See paragraph 9.1 General considerations for further details.

9.7 Secondary Outcome Analyses

See paragraph 9.1 General considerations for details.

9.8 Teriary Outcome Analyses

See paragraph 9.1 General considerations for details.

9.9 Exploratory Endpoint Analyses

Speech in noise data will be assessed for the total population and separately for the individual sites. Data will be tabulated for comparison, no statistical analysis will be performed.

9.10 Safety Analyses

Primary safety analysis will be performed at 3 months post-surgery.

9.10.1 Implant site evaluation (numbness)

Implant site evaluation (numbness) will be summarised by frequency and percent of 1. No numbness, 2. Numbness over the implant Magnet Assembly area and 3. Numbness over the implant Magnet Assembly area and 2 cm outside the implant Magnet Assembly area by visit.

9.10.2 Adverse events

Separate tabulations of AEs, ADEs, SAEs, SADEs and AESIs will be produced. AEs, ADEs and AESIs will also be produced by severity (mild, moderate or severe) and relationship (related defined as Possibly, Probably and Definitely related). Adverse events will be coded and summarized by number of events and also by number of subject and percent with events.(see section 11.2)

9.10.3 Device deficiency

DDs will be reported by visit as described in 11.3 General considerations.

9.10.4 Concomitant medication

Concomitant medications will be defined as start or end date from surgery to end of study and will be presented by listings.

9.11 Interim Analyses

Not applicable.

10 INFORMED CONSENT PROCESS

The Investigator shall obtain written informed consent from the subject using an approved ICF prior to any clinical investigation related examination or activity. The rationale of the clinical investigation, as well as the risks and benefits, what participation will involve, and alternatives to participation will be explained to the subject. Ample time will be provided for the subject to enquire about details of the clinical investigation and to decide whether to participate.

All questions about the clinical investigation shall be answered to the satisfaction of the subject or the subject's legally acceptable representative. Subjects shall not be coerced or unduly influenced to participate or to continue to participate in a clinical investigation.

Each subject (or their legally authorised representative) and the person who conducted the informed consent discussion, shall sign and date the Informed Consent Form (ICF). Where required, a witness shall sign and personally date the ICF. A copy of the signed ICF shall be given to the subject. The original signed ICF shall be archived in the Investigator's Site File or subject file at the investigational site.

The subject, or the subject's legally authorised representative, shall be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the clinical investigation. The communication of this information must be documented as an update to the ICF and re-consent of the subject.

11 ADVERSE EVENTS AND DEVICE DEFICIENCIES

11.1 Definitions

11.1.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons whether or not related to the medical device or the procedures required for implant or use.

NOTE 1: This definition includes events related to the medical device or the comparator device.

NOTE 2: This definition includes events related to the procedures involved.

NOTE 3: For users and other persons, this definition is restricted to events related to medical devices.

11.1.2 Adverse Device Effect

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

NOTE 1: This includes any AE resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the medical device.

NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the medical device.

11.1.3 Serious Adverse Event

A serious adverse event (SAE) is any AE that:

- led to a death,
- led to a serious deterioration in the health of the subject that either resulted in:
  - a life-threatening illness or injury, or
  - a permanent impairment of, or damage to, a body structure or a body function, or
  - in-patient hospitalisation or prolonged hospitalisation, or
  - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment or damage to a body structure or a body function, or
  - Chronic disease.
- led to foetal distress, foetal death or a congenital physical or mental abnormality, or birth defect

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

11.1.4 Serious Adverse Device Effect

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

11.1.5 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 Investigator's Brochure (7).

NOTE: An anticipated serious adverse device effect is an effect, which by its nature, incidence, severity, or outcome has been identified in the Investigator's Brochure (7).

11.1.6 Adverse Events of Special Interest

The following AEs are defined as adverse events of special interest (AESIs) and should be reported within 24 hours, after being aware of an event:

- AE that interferes with the daily use of the medical device(s)
- AE at the site of the implant that leads to
    - Revision surgery including explantation
    - Severe soft tissue complication
    - Prescription of antibiotics

11.1.7 Device Deficiency

A DD is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance.

NOTE: Device Deficiencies include malfunctions, use errors, and inadequate labelling or information supplied by the manufacturer.

11.2 Recording and Handling of Adverse Events

Subjects shall be carefully monitored during the clinical investigation and the investigator should enquire about AEs at each visit.

All AEs will be recorded from Screening/Baseline. AE recording will continue for each subject until completion of the final visit. Ongoing SAEs, SADEs and/or AESI will be followed for 30 days, or until resolution or stabilisation of the event, whichever comes first.

Source notes should indicate the evaluation for AEs, even if none to report. All required AEs will be reported if observed, even if anticipated and/or acknowledged as a risk factor in the consent.

All AEs will have the following information documented: start and stop dates, action taken, outcome, severity and investigators opinion on the potential relationship to the Investigational device and investigational procedures. If an AE changes in severity, the most severe (highest) grade will be captured for that event on the Adverse Events CRF.

Adverse events will be summarized by CTCAE to System Organ Class (SOC) and CTCAE term.

11.2.1 Assessment of Severity

The Principal Investigator (or qualified delegate) will make an assessment of severity for each event based on clinical judgement. The intensity of each event recorded in the CRF should be assigned to one of the following categories:

Mild	An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
Moderate	An event that is sufficiently discomforting to interfere with normal activities
Severe	An event which is incapacitating and prevents normal everyday activities

11.2.2 Assessment of Causality

The Investigator will assess the potential causal relationship of each event, using clinical judgement. Alternative causes, such as natural history of underlying diseases, other risk factors and the temporal relationship of the event to the IMD product will be considered and investigated. The causal relationship to the IMD is to be assessed by the Investigator (or medically qualified delegate) and should be assessed using the following classifications:

Not related	Relationship to the medical device or procedures can be excluded when: • the event is not a known side effect of the product category the device belongs to or of similar devices and procedures; • the event has no temporal relationship with the use of the device or the procedures; • the event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; • the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the event; • the event involves a body-site or an organ not expected to be affected by the device or procedure; • the event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); • the event does not depend on a false result given by the Investigational device used for diagnosis, when applicable; • harms to the subject are not clearly due to use error; In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the event.
Unlikely related	The relationship with the use of the medical device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

Possibly related	The relationship with the use of the medical device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possibly related.
Probably related	The relationship with the use of the medical device seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.
Definitely related	The event is associated with the medical device or with procedures beyond reasonable doubt when: • the event is a known side effect of the product category the device belongs to or of similar devices and procedures; • the event has a temporal relationship with the medical device use/application or procedures; • the event involves a body-site or organ that – the medical device or procedures are applied to – the medical device or procedures have an effect on; • the event follows a known response pattern to the medical device (if the response pattern is previously known); • the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the event (when clinically feasible); • other possible causes (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; • harm to the subject is due to error in use; • the event depends on a false result given by the medical device used for diagnosis, when applicable; In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the event.

11.2.3 Assessment of Seriousness

The Investigator will assess the seriousness of each event according to clinical judgement and the definition provided in section 11.1.3.

11.2.4 Assessment of Expectedness

An event should be considered unanticipated if the nature, severity, or frequency of that event is not consistent with the applicable safety reference information, such as the risk analysis report, hazards analysis, IB, or Product Information/IFU if the product is approved for marketing.

For this clinical investigation the listed items in Section 0 and 8.3of this CIP and/or the Investigator's Brochure are anticipated ADEs.

Anticipated	An adverse device effect (ADE) which by its nature, incidence, severity, or outcome is consistent with the applicable safety reference information (e.g., IB, IFU).
Unanticipated	An adverse device effect (ADE) which by its nature, incidence, severity, or outcome is not consistent with, or has not been identified in the applicable safety reference information (e.g., IB, IFU).

11.3 Recording and Handling of Device Deficiencies

Subjects shall be carefully monitored during the clinical investigation and routinely questioned about DDs at each visit. Source notes should indicate the evaluation for DDs, even if none to report.

The investigator shall assess if the DD led to an AE or could have led to a serious medical occurrence (serious adverse device effect) if;

a) suitable action had not been taken,

b) intervention had not been made, or,

c) circumstances had been less fortunate

Device deficiencies will be reported for all devices supplied by the Sponsor and will be documented in the source notes and the DD page of the CRF.

All explanted implants shall be sent to Device Analysis according to company procedures. Implants should be sent to CLTD and Sound Processors to CBAS.

In case of any DD and/or explantation of an implant, site should contact the sponsor, whom will then provide the site with a RETRIEVED DEVICE KIT for return of the implant and further instructions on the return process. In case of any DD of an Sound Processor the site should contact the sponsor for further return details.

11.4 Reporting Responsibilities

The Investigator is responsible for reporting all AEs and DDs in the CRF.

11.4.1 Investigator Reporting of Serious Adverse Events

All AEs meeting the criteria for an SAE, or DD that could have led to an SADE, must be reported to the Sponsor in accordance with timeframes required by local regulations, as follows:

Country	Timeframe
AUSTRALIA	24 h
HONG KONG SPECIAL ADMINISTRATIVE REGION OF THE PEOPLE'S REPUBLIC OF CHINA	24 h

Reporting is achieved through completion of the events details in the Adverse Event page of the eCRF

The investigator shall always provide an assessment of causality at the time of the initial report, as described in section 11.2.2 'Assessment of Causality'. If data obtained after reporting indicates that the assessment of causality is incorrect, then the SAE form may be appropriately amended, signed, dated, and resubmitted to the Sponsor.

If the investigator does not have all other information regarding an SAE, he/she will not wait to receive additional information before reporting the event. The reporting forms shall be updated when additional information is received.

The investigator is responsible for reporting of safety events to their local EC using the applicable report form, in accordance with local regulations.

11.4.2 Sponsor Notification of Events

The Sponsor is responsible for reviewing all safety data to evaluate potential causality and anticipation of all ADEs.

The Sponsor is also responsible for reporting all reportable events according to the requirements and timelines of the regulatory authorities relevant to this clinical study, and shall conduct an expedited assessment of all SAEs, unanticipated ADEs, DDs that could have led to an SADE and AESI.

The Safety Monitor for AE/DD assessment and any AE/DD related queries is:

Name Sponsor Safety Monitor:	[redacted]
Country:	[redacted]
Phone number:	[redacted]
E-mail:	[redacted]

11.5 Independent Data Monitoring Committee

Not applicable.

12 Device Accountability

Access to investigational devices shall be controlled and the devices shall be used only in the clinical investigation and according to this CIP.

The Principal investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices, which shall include

a) the date of receipt

b) identification of each investigational device (batch number/serial number or unique code)

c) the expiry date, if applicable

d) the date of use

e) subject identification

f) date on which the investigational device was returned/explanted from subject

g) the date of return of unused, expired or malfunctioning of the investigational device

Contact information regarding the investigational device is provided below.

Name of contact person of the Sponsor:	[redacted]
Country and time zone:	[redacted]
Phone number:	[redacted]
Email:	[redacted]

13 DEVIATIONS FROM THE CLINICAL INVESTIGATION PLAN

The investigator(s) must not deviate from the CIP, except in case of an emergency to protect the safety and well-being of the subject(s). Such deviations will be documented by the site personnel in the source documentation for the subject and reported to the relevant EC as per institutional requirements and to the Sponsor as soon as possible.

If there is a deviation from CIP-defined assessments or parts thereof are omitted or completed incorrectly, the deviation will also be documented by the site personnel in the source documentation for the subject. Depending on the type or severity of the deviation the Investigator may be required to notify the EC, particularly if the deviation potentially impacts subject safety, performance of Investigational device, or data integrity.

All CIP deviations will be documented in the eCRF to enable analysis and reporting by the Sponsor in the Clinical Investigation Report CIR, or to the relevant regulatory authority(s), if applicable.

Gross misconduct on behalf of an Investigator, such as intentional non-compliance with CIP or GCP requirements or fraud, will result in disqualification of the Principal Investigator and/or Site from participation in the investigation. Data provided by the Principal Investigator or Site will be excluded from the per-protocol analysis group.

14 DATA MANAGEMENT

The CRF will capture subject status according to the following criteria:

- Consented: Signed consent and eligibility evaluations underway

- Screen Fail: Subject determined not to be eligible to proceed for participation
- Enrolled: First use of the Investigational device following completion of screening activities and confirmation of eligibility
- Withdrawn: Enrolled subjects who withdraw or are withdrawn by the Investigator or Sponsor before the expected last visit.
- Complete: Enrolled subjects who complete the planned follow up visits according to this CIP.

Source data will be captured in clinic notes, paper-based source data worksheets, or printed directly from testing software. Before initiation of the clinical investigation the PI should together with the CRA complete the template “Origin of source data” stipulating were source data should be recorded at the investigation site. If electronic medical records do not permit read only access for monitoring purposes, a verified printout must be provided.

Data collection will be performed using [redacted] for electronic data capture (EDC) on electronic Case Report Forms (eCRFs). Site staff will be trained on the completion of the eCRFs prior to obtaining access to the system, and will have their own Login/Password. Access to clinical investigation information will be based on an individual’s role and responsibilities.

[redacted] uses role-based user permissions for data entry, viewing, and reporting options. All communications between users and the EDC server are encrypted. Web servers are protected by a managed firewall. This application is designed to be in compliance with applicable regulations including 21 CFR Part 11.

The application will include programmed data consistency checks and supports manual generation of data clarifications/queries, including documentation of site responses. The application maintains a comprehensive audit trail for all data entered, including updates and queries, and documents the time that each entry occurred and who made the entry.

Principal Investigators will affirm that the data for each subject at their site is accurate and complete by way of an electronic signature.

In addition, de-identified electronically generated data will be collected from the OFS. The unamended data file shall be regarded as the source.

15 CONFIDENTIALITY

The investigator and site staff will collect and process personal data of the subjects in accordance with governing data privacy regulations [such as the EU GDPR regulations].

Data will be reported to the Sponsor on CRFs or related documents (for example, questionnaires). Subjects will be identified on CRFs and other related documents only by a unique subject identification code and shall not include the subject’s name or other personal identifiable information. Completed CRFs or related documents are confidential and will only be available to the Investigator and site staff, the Sponsor and their representatives, and if requested to the Ethics Committee and national regulatory authorities. Publications or submission to a regulatory authority shall not disclose the identity of any subject.

16 ETHICS COMMITTEE APPROVAL

The clinical investigation will not commence prior to the written favourable opinion or approval from the EC is obtained.

The final Sponsor-approved version of the CIP, Informed Consent Form, and other necessary documents shall be submitted to the EC. A copy of the EC opinion/approval shall be provided to the Sponsor.

The Investigator shall forward to the Sponsor, for review and approval, any amendment made to the approved ICF and any other written information to be provided to the subject prior to submission to the EC.

The Sponsor and Principal Investigator will continue communications with the EC, as required by national regulations, the clinical investigation plan, or the responsible regulatory authority.

Any additional requirements imposed by the EC or regulatory authority will be implemented by the Sponsor.

The Investigator shall submit the appropriate documentation if any extension or renewal of the EC approval is required. In particular, substantial amendments to the CIP, the ICF, or other written information provided to subjects will be approved in writing by the EC.

The Investigator shall report to the EC any new information that may affect the safety of the subjects or the conduct of the clinical investigsation. The Investigator will send written status summaries of the clinical investigation to the EC regularly, as per local EC requirements.

Upon completion of the clinical investigaton, the Investigator shall provide the EC with a brief report of the outcome of the clinical investigation, as per local EC requirements.

The clinical investigation is covered by clinical trial insurance, meeting the requirements of the participating countries.

17 SUSPENSION OR PREMATURE TERMINATION

The Sponsor will discontinue the clinical investigation site if:

1) major non-adherence to the CIP or GCP principles is occurring
2) it is anticipated that the subject recruitment will not be adequate to meet the objectives of the clinical investigation

An ongoing clinical investigation may be discontinued in case of:

1) device failure
2) serious or intolerable ADE, leading to the explant or discontinued use of the device
3) subject's death

Should the Sponsor discontinue the clinical investigation, the Sponsor will continue to support those subjects who were already implanted with the device under investigation according to the clinical investigation research agreement.

18 AMENDMENTS TO THE CLINICAL INVESTIGATION PLAN

No changes in the CIP or investigational procedures shall be made without mutual agreement of the Coordinating Investigator and the Sponsor. This agreement will be documented as a CIP amendment. Amendments will require notification to the Ethics Committees (ECs) by the Principal Investigators (and to the relevant regulatory authority(s) by the Sponsor, if applicable).

19 RECORD KEEPING AND RETENTION

Data generated from the clinical investigation will be stored in a limited-access file area and be accessible only to representatives of the investigation site, the Sponsor and its representatives, and relevant health authorities/regulatory agencies. All reports and communications relating to investigation subjects will identify subjects only by subject unique identification code. Complete subject identification will be maintained by the Investigator. This information will be treated with strict adherence to professional standards of confidentiality.

The investigator must retain clinical investigation related records in accordance with the period required by local regulation, as follows:

Country	Retention period
AUSTRALIA	According to local regulation
HONG KONG SPECIAL ADMINISTRATIVE REGION OF THE PEOPLE'S REPUBLIC OF CHINA	According to local regulation

The Sponsor will notify the Principal Investigator when records are no longer needed. The Investigator will not discard any records without notifying the Sponsor. If the Principal Investigator moves from the current investigation site, the Sponsor should be notified of the name of the person who will assume responsibility for maintenance of the records at the investigation site or the new address at which the records will be stored. The Investigator will notify the Sponsor as soon as possible in the event of accidental loss or destruction of any investigation documentation.

20 PUBLICATION POLICY

This clinical investigation will be prospectively registered at a public clinical trial registry for example ClinicalTrials.gov.

A joint peer-reviewed publication authored by the clinical investigator(s) and Sponsor will be prepared. In addition, the results of the clinical investigation may also be disseminated as conference presentations (e.g., abstract and poster session). Manuscript authorship and responsibilities will be discussed and agreed upon prior to clinical investigation start and in accordance with guidelines and recommendations provided by the International Committee of

Medical Journal Editors (ICMJE) to enable communication in a timely manner. All contributors who do not meet the criteria for authorship will be listed in an acknowledgments section of the publication.

21 STATEMENTS OF COMPLIANCE

This clinical investigation shall be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki, International Standard ISO 14155 Clinical investigation of medical devices for human subjects - Good Clinical Practice, and any regional or national regulations, as applicable.

22 QUALITY CONTROL AND ASSURANCE

In accordance with Cochlear's Quality Management System, all clinical investigations shall be conducted according to internationally recognised ethical principles for the purposes of obtaining clinical safety and performance data about medical devices.

The Sponsor employees (or designee) shall use standard operating procedures (SOP) to ensure that clinical investigation procedures and documentation are consistently conducted and compliant with the ISO 14155 Standard, Good Clinical Practice (GCP), and applicable local regulations.

22.1 Monitoring

The Sponsor will perform on-site and remote monitoring visits as frequently as necessary to oversee conduct, data collection and record keeping by sites. The clinical investigation monitoring plan is a separate document describing all the activities performed during site qualification, initiation, monitoring, and close out.

22.2 Audits

An Investigator must, in reasonable time, upon request from a relevant health authority or regulatory agency, permit access to requested records and reports, and copy and verify any records or reports made by the Investigator. Upon notification of a visit by a regulatory authority, the Investigator will contact the Sponsor immediately.

The Investigator will grant the Sponsor representatives the same access privileges offered to relevant health authority or regulatory agents, officers, and employees.

23 TRADEMARKS AND COPYRIGHT

24 REFERENCES

1. **World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. 2013. Available at: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-h.**

2. International Organization for Standardization. ISO 14155:2011 Standard: Clinical investigation of medical devices for human subjects – Good clinical practice. 2011. Available at: https://www.iso.org/obp/ui/#iso:std:iso:14155:ed-2:v1:en.

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25 CHANGE HISTORY

Version	Change	Rationale
2.0	Section 7.1.1, 7.3.2.2 Speech in Noise test to be used in Australia changed from HINT to AuSTIN. Section 9.9 Exploratory analysis added in connection to this.	At the site qualification visits, both Sydney and Melbourne indicated that it would be possible to use HINT when performing Speech in Noise assessment. However, at the site initiation visit (SIV) at SCIC in Sydney it was discovered that no HINT test was available. The study team also realised that the Speech in Noise test at the site HEARing CRC in Melbourne was not performed according to the HINT method explained during the Site Initiation visit. There is no HINT with Australian speech available, only with American speech which would be difficult for the test subjects to understand completely. It was therefore agreed that the sites in Australia shall use the AuSTIN test for Speech in Noise assessment, since it is a validated method in Australia and available at both sites.

APPENDICES

APPENDIX 1: CONFORMITY STATEMENT

Document will be provided separately as Appendix.