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

NCT Number: **NCT04754477**

Document Date: **19 January 2021**

Clinical Investigation Plan

Investigation Title: A multicentre, open, long-term clinical investigation evaluating safety, performance and Patient Reported Outcomes with an Active Osseointegrated Steady-State Implant System in adult subjects with conductive hearing loss, mixed hearing loss or single-sided sensorineural deafness.

Short Tile:	**LoTeOS**
CIP Number:	**CBAS5793**
Version Number:	**3.0**
Date:	**19-JAN-2021**
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	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 Stigbergsliden 5 Göteborg 414 63 SWEDEN
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 Investigational 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**
[redacted]	[redacted]
Signature	**Date**

INVESTIGATOR AGREEMENT

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**
[redacted]	[redacted]
Signature	**Date**

INVESTIGATOR AGREEMENT

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**
[redacted]	[redacted]
Signature	**Date**

TABLE OF CONTENTS

1 DEFINITIONS AND ABBREVIATIONS

Term	Description
ADE	Adverse Device Effect
AE	Adverse Event
AESI	Adverse Event of Special Interest
APHAB	Abbreviated Profile of Hearing Aid Benefit
AuSTIN	Australian Sentence Test in Noise
CBAS	Cochlear Bone Anchored Solutions AB
CDI	Cochlear Device Image
CHL	Conductive Hearing Loss
CIP	Clinical Investigation Plan
CMR	Controlled Market Release
CRF	Case Report Form
CRO	Contract Research Organisation
CSRI	Client Service Report Inventory
DD	Device Deficiency
EC	Ethics Committee Synonymous abbreviations/terms include: 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
HARL	Hearing Aid Research Lab
HRQoL	Health Related Quality of Life
HUI	Health Utilities Index
GCP	Good Clinical Practice
ICF	Informed Consent Form
IFU	Instruction For Use
IMDRF	International Medical Device Regulators Forum
ISO	International Organization for Standardization
MHL	Mixed Hearing Loss
OFS	Osia Fitting Software
OTE	Off-The-Ear (sound processor)
PI	Principal Investigator

Term	Description
PSSRU	Personal Social Service Research Unite
PTA	Pure Tone Average
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 multicentre, open, long-term clinical investigation evaluating safety, performance and Patient Reported Outcomes with an Active Osseointegrated Steady-State Implant System in adult subjects with conductive hearing loss, mixed hearing loss or single-sided sensorineural deafness.
Short title	LoTeOS
Investigation number	CBAS5793
Name of investigational medical device(s)	Active Osseointegrated Steady-State Implant System (OSI)
Intended use of investigational medical device(s)	The Cochlear Osia 2 System uses bone conduction to transmit sounds to the cochlea (inner ear) with the purpose of enhancing hearing. The Osia System is intended for adults and children (no minimum age limit) with conductive or mixed hearing loss (up to 55 dB HL) and single-sided sensorineural deafness (SSD), with a body weight of 7 kg* or more and sufficient bone quality and quantity to support successful implant placement. *due to the potential presence of residual ethylene oxide after sterilisation of the device.
Name and description of comparator device/product(s)	Not applicable
Expected start date (first subject consented)	Feb-2021
Expected recruitment period	4 months
Expected duration per subject	12 months
Expected total duration of the clinical investigation	17 months
Number of subjects planned	Maximum 27
Number of investigational sites planned	3
Inclusion criteria	1. Subject has performed Hearing assessment at 3 and/or 6 months in the clinical investigation CBAS5751 2. Willing and able to provide written informed consent
Exclusion criteria	1. 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 2. Use of ototoxic drugs that could be harmful to the hearing, as judged by the investigator

Objectives and Endpoints	
Safety Objectives	**Endpoints**
Collect long term safety data	• Number and type of reported Adverse events (including explantations, revision surgery) • Number and type of reported Device deficiencies • Use of concomitant medication • Socio-economic data and health care utilisation related to hearing rehabilitation
Compare baseline audiogram before implantation with audiogram at follow up visits to investigate if the thresholds have been constant over time	At 12 and 24 months: • Bone and air conduction thresholds, masked and unmasked
Performance Objectives	**Endpoints**
Collect and evaluate long term data on Device and Hearing Performance and compare it with the last performed measurement (3 or 6 months) in the clinical investigation CBAS5751	At 12 and 24 months compared to last performed measurement (3 or 6 months) in CBAS5751: • Thresholds audiometry, sound-field [PTA4, Mean of 0.5, 1, 2 and 4 kHz] • Thresholds audiometry, sound-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] • BC-direct
Patient Reported Outcomes Objectives	**Endpoints**
Collect and evaluate long term data on Patient Reported Outcomes and compare it with the last performed assessment (3 or 6 months) in the clinical investigation CBAS5751	At 12 and 24 months: • Self-reported assessments of hearing outcome: ➢ Abbreviated Profile of Hearing Aid Benefit (APHAB) ➢ Speech, Spatial and Qualities of Hearing Scale (SSQ) • Health-related quality of life (HRQoL) ➢ Health Utilities Index (HUI)
Collect Subjective experience of the investigational device and sound experience	At 12 and 24 months self-reported assessment of: • Satisfaction with the investigational device • Experienced sound quality of the investigational device
Collect long term usability data and compare it with the last performed assessment (3 or 6 months) in the clinical investigation CBAS5751	At 12 and 24 months: • Daily use • Daily streaming time • Battery lifetime • Magnet choice / Magnet change(s) required

	(and why?) • Use of SoftWear pad • Sound Processor retention • Sound Processor wearing comfort
Exploratory Objective	**Endpoint**
Collect high frequency thresholds with the device using the CDI tool	At 12 and 24 months: • Thresholds audiometry [at 6.0, 7.0, 8.0, 9.0 and 9.5 kHz]

3 SCHEDULE OF EVENTS

Visit Type	**Screening/Visit 1**	**EOS**
Timing of Investigation	**12M post-surgery**	**24M post-surgery**
Visit window (±)	**± 22 weeks**	**± 4 weeks**
Procedures		
Written informed consent	X	
Demographics (transfer from CBAS5751)		
Eligibility	X	
Audiogram	X	X
Sound processor fitting:		
• Coil to coil measurement	X	X
• BC direct	X	X
• Fine tuning	X [a]	X [a]
Blocking verification	X	X
Free field thresholds	X	X
Speech recognition in noise	X	X
High frequency thresholds	X	X
APHAB	X	X
SSQ	X	X
HUI	X	X
Satisfaction with the device	X	X
CSRI [b]	X	X
Usability:		
Daily use	X	X
Daily streaming time	X	X
Battery lifetime	X	X
Magnet choice	X	X
Use of Soft Wear pad	X	X
Retention	X	X
Comfort	X	X
Concomitant Medications [c]	X [d]	X
Adverse Events	X [d]	X
Device Deficiencies	X [d]	X
Device exposure	X	X
Extra visits as needed		

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

CSRI, Client Service Receipt Inventory

[a] *Should be performed if needed.*

[b] *Investigates economic consequences of hearing rehabilitation by capturing major health care costs and productivity losses.*

[c] *Specify what types of concomitant therapies are applicable e.g. prescription medications, over-the-counter medications, vitamins, and herbal supplements, and non-pharmacologic therapies such as [insert any other relevant therapies such as acupuncture, electrical stimulation, special diets and exercise regimens].*

[d] *From the 6-months visit in the CBAS5751 clinical investigation up to the 12-months visit.*

4 BACKGROUND INFORMATION AND RATIONALE

4.1 Introduction

The aim of this investigation is to collect long-term safety and performance data with the Active Osseointegrated Steady-State Implant System, Cochlear™ Osia® 2 System, by following subjects from the previous Osia clinical investigation CBAS5751. This is to meet expected requirements from any Notified Body or Regulatory agency. In addition, questions regarding device satisfaction, sound satisfaction, usability and health care utilisation will be asked. This data can be used for current and future comparison with other studies, and for supporting marketing claims.

4.2 Findings of Previous Nonclinical and Clinical Studies

4.2.1 Nonclinical Data

Results from technical verification and validation activities are described in the currently released Investigator's Brochures (3) (4).

4.2.2 Clinical Data

The Osia 2 system has been tested for 6 months in the recently completed prospective, multicentre clinical investigation, CBAS5751, including 29 subjects with CHL, MHL or SSD (see section 4.2.2.1) (5).

In addition, a Controlled Market Release (CMR) and early post-launch surveillance activity have been conducted on the Osia 2 System in the United States of America (6) following FDA approval on November 15th 2019 (see section 4.2.2.2).

4.2.2.1 Multicentre Clinical Investigation with the Osia 2 System

Safety and performance of the Osia 2 System were studied in a prospective, multicentre clinical investigation CBAS5751 (ClinicalTrials.gov Identifier NCT 04041700) including 29 adults with CHL (n=12), MHL (n=12), or SSD (n=5) (5). Subjects were unilaterally (n=28), or bilaterally (n=1) implanted and served as their own controls (i.e. pre-operative unaided hearing vs. aided hearing with the Osia 2 System). The subjects completed the primary efficacy and safety endpoints at 3 months, and data collection continued until investigation ended at 6 months.

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 2 System provided statistically significant improvements in hearing performance compared to the unaided condition with an improvement in hearing thresholds at 3 and 6 months (PTA4, mean of 0.5, 1, 2, and 4 kHz) of -27.3, dB (SD 8.7 dB, range -46.3 to -10.0 dB), and -28.4 dB HL (SD=9.6, range -46.3 to -10.0 dB HL) respectively.

Statistically significant improvements were also seen for 'Speech recognition in quiet' at all speech presentation levels (SPL), 50, 65 and 80 dB SPL and for 'Adaptive speech recognition in noise', at all timepoints.

For ‘Speech recognition in quiet’ at 50 dB SPL the improvements were 62.7 percentage points (SD: 20.7, range 22.0 to 88.0), and 62.3 percentage points (SD 22.1, range -4.0 to 84.0) at 3 and 6 months respectively.

At 65 dB SPL the improvements were 55.5 percentage points (SD 29.3, range 10.0 to 96.0) and 54.0 percentage points (SD 29.8, range -6.0 to 98.0) at 3 and 6 months, respectively.

At 80 dB SPL the improvements were 23.7 percentage points (SD 27.7, range -6.0 to 96.0, $p<0.0001$) and 24.3 percentage points (SD 28.0, range -7.0 to 92.0), at 3 and 6 months, respectively.

For ‘Adaptive speech in noise’ mean improvements in SNR with the Investigational device compared to unaided was -9.1 dB (SD 7.9 dB, range -21.8 to 1.6 dB) and -8.8 (SD 7.9 range -21.8 to 1.4) at 3 and 6 months respectively.

All SSQ subscales (Total, Speech, Spatial, and Quality) showed statistically significant improvements ($p<0.0001$) at both 3 and 6 months. APHAB scores showed statistically significant improvements ($p<0.001$) at both 3 and 6 months for the subscales Ease of Communication (EC), Background Noise (BN), the Global score and Reverberation (RV). Health status and health related quality of life, measured with HUI3, showed statistically significant improvements for the attributes Comprehensive health state ($p=0.0052$) and Emotion attribute ($p=0.033$) at 3 months, and for the attributes Comprehensive health state ($p=0.0093$) and Hearing ($p=0.045$) at 6 months.

4.2.2.1.2 Safety

In total, 54 AEs were reported in 22 (75.9%) of the 29 implanted subjects during the investigation. Fifty-one (51) of the fifty-four (54) events were classified as mild. Twenty-seven (27) events were judged as related to either the device (5 events), the procedure (12 events) or both device and procedure (10 events).

Four (4) *Serious Adverse Events* (SAEs) were reported within the six months investigational period. One (1) event was judged as probably related to both the device and the procedure, and one as probably related to the procedure. Both were recorded as post-operative wound infections in the perioperative phase and were resolved after hospitalisation. The other two SAEs occurred in the same subject and were judged as not related to the device nor the procedure.

Overall, eighty-nine (89) Device deficiencies (DDs) were reported for twenty-two (22) of the subjects during the 6 months investigation period. Of these, 79% (n=70) were described as related to the SP, 12% (n=11) to the OFS, 8% (n=7) to accessories and 1% (n=1) to the implant.

4.2.2.2 Controlled Market Release Osia R4 and Post Launch Surveillance

The objective of the CMR was to gain experience in various aspects of the Osia 2 System through the collection of observational and clinical experience data in the form of surveys, both through Field staff and Clinicians (6). The CMR was not aimed at providing clinical performance or clinical benefit data from patients, but rather usability among clinicians and safety during surgery. Twenty-three (23) surgeons performed 44 surgeries in 16 clinics on 43 recipients (1 bilateral). Five (5) complications were report: One (1) case of exposed dura and excessive bleeding (puncture of the transverse sinus), the BI300 implant was able to be implanted without further complication, two (2) post-operative wound infections, both treated successfully with antibiotics and two (2) post-operative hematomas over the coil site. One resolved via application of ice and the other was treated by needle aspiration.

4.3 Investigation Rationale

The rationale for conducting this clinical investigation is to collect long-term safety and performance data of the Osia 2 System, to fulfill expected requirements from any Notified Body or Regulatory agency. The investigation will follow subjects from the previous Osia clinical investigation CBAS5751 up to two years after implantation and similar endpoints as in that investigation will therefore be chosen. In addition, answers on questions regarding device satisfaction, sound satisfaction, usability and health care utilisation will be collected for current and future comparison with other studies. For further development of the devices and to increase knowledge and understanding of high frequency hearing thresholds with the Osia implants on recipients, measurements of high frequency thresholds will be included. Currently no bone conduction data is available on the hearing threshold above 6kHz when stimulated on the Osia position after implantation.

5 MEDICAL DEVICE INFORMATION

5.1 Identity and Description of the Investigational Medical Device (IMD)

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 (Table 1). The internal part is an implant made up of a receiver coil and the actuator (vibrator) 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.

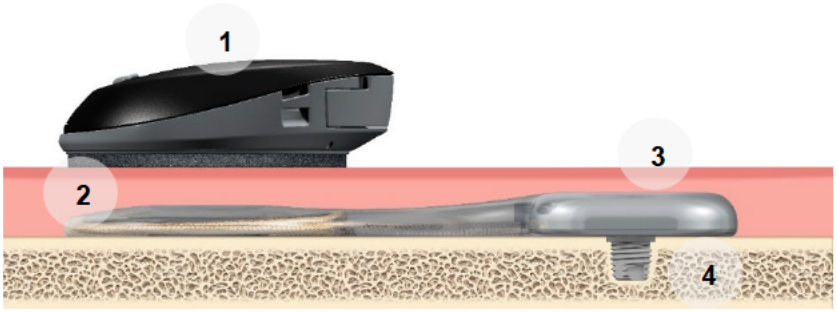

Figure 1: The Osia 2 System consisting of Osia 2 Sound Processor and OIS200 Implant.

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.

Table 1: List of parts of the Investigational device.

Part Number	Name	Description	Regulatory approval details (certification date)
P1170466	Cochlear™ Osia® OSI200 Implant	OSI200 Implant	**EU:** not currently CE-marked **US:** Class II (Nov 2019) **Canada:** Class III (Jun 2020)
P1233400	Cochlear™ Osia® 2 Sound Processor Kit	includes: one SP base, all five covers, one programming front and one inner case and Tamperproof tool in one package	**EU:** AIMDD; Class III (May 2020) **US:** Class II (Nov 2019) **Canada:** Class III (Jun 2020)
P1343790 P1343791 P1343793	Cochlear™ Osia® 2 Sound Processor Magnet pack	strength 1, 4 pcs strength 2 & 3, 1+1 pcs strength 4, 4 pcs	**EU:** MDR; Class I (Jul 2020) **US:** Class II (Nov 2019) **Canada:** Class III (Jun 2020)
92128 92129	BI300 Implant	The BI300 Implant is available in 2 lengths (3 and 4 mm)	**EU:** MDD; Class IIb (Jan 2010)* **US:** Class II **Canada:** Class III (AUS / HK: Class II / Class III)

** The Baha BI300 Implant was approved for use with the Osia System in 2018 (TÜV SÜD) and in 2019 (FDA).*

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 coil, magnet assembly and the implant body.

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

5.1.3 The Osia 2 Sound Processor (Osia 2 SP)

The Osia 2 SP is a button-type SP, worn off-the-ear (OTE) (Figure 2), 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 Nucleus® Safety Line and Cochlear 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.

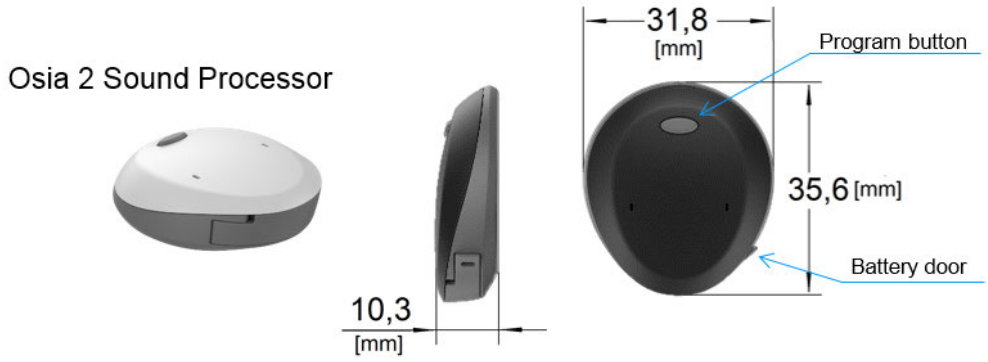

Figure 2. The Osia 2 Sound Processor.

5.1.4 Osia 2 Sound Processor Magnets

The Osia 2 Sound Processor Magnets are available in 4 different strengths; 1 being the weakest and 4 the strongest.

5.1.5 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.

The IMD and/or the packaging for the device will state that the device is exclusively for use in a clinical investigation.

5.2 Identity and Description of the Comparator

Not applicable

5.3 Accessory Device Requirements

5.3.1 Accessories

In the previous CBAS5751 investigation the following other approved accessories were distributed by 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 P793406).
- 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), version 2. 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 Cochlear Device Image (CDI) tool

To measure the high frequency in-situ thresholds with the implant the engineering software, CDI tool version 4, will be used. Communication between the computer-based software and the sound processor is achieved using a Hi-Pro 2 programming unit. The CDI tool is developed by Cochlear Limited, Sydney, Australia and used during product development to program the sound processor and includes detailed controls for stimulus generation.

6 OBJECTIVES

6.1 Safety Objectives

Safety Objectives	Endpoints
Collect long term safety data	• Number and type of reported Adverse events (including explantations, revision surgery) • Number and type of reported Device deficiencies • Use of concomitant medication • Socioeconomic data and health care utilisation related to hearing rehabilitation
Compare baseline audiogram before implantation with audiogram at follow up visits to investigate if the thresholds have been constant over time	At 12 and 24 months: • Bone and air conduction thresholds, masked and unmasked

6.2 Performance Objectives

Performance Objectives	Endpoints
Collect and evaluate long term data on Device and Hearing Performance and compare it with the last performed measurement (3 or 6 months) in the clinical investigation CBAS5751	At 12 and 24 months compared to last performed measurement (3 or 6 months) in CBAS5751: • Thresholds audiometry, sound-field [PTA4, Mean of 0.5, 1, 2 and 4 kHz] • Thresholds audiometry, sound-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] • BC-direct

6.3 Patient Reported Outcomes Objectives

Patient Reported Outcomes Objectives	Endpoints
Collect and evaluate long term data on Patient Reported Outcomes and compare it with the last performed assessment (3 or 6 months) in the clinical investigation CBAS5751	At 12 and 24 months: • Self-reported assessments of hearing outcome: ➢ Abbreviated Profile of Hearing Aid Benefit (APHAB) ➢ Speech, Spatial and Qualities of Hearing Scale (SSQ) • Health-related quality of life (HRQoL) ➢ Health Utilities Index (HUI)
Collect Subjective experience of the investigational device and sound experience	At 12 and 24 months self-reported assessment of: • Satisfaction with the investigational device • Experienced sound quality of the investigational device
Collect long term usability data and compare it with the last performed assessment (3 or 6 months) in the clinical investigation CBAS5751	At 12 and 24 months: • Daily use • Daily streaming time • Battery lifetime • Magnet choice / Magnet change(s) required (and why?) • Use of SoftWear pad • Sound Processor retention • Sound Processor wearing comfort

6.4 Exploratory Objective

Exploratory Objective	Exploratory Endpoint
Collect high frequency thresholds with the device using the CDI tool	At 12 and 24 months: • Thresholds audiometry [at 6.0, 7.0, 8.0, 9.0 and 9.5 kHz]

7 DESIGN OF THE CLINICAL INVESTIGATION

7.1 General

This is a multicentre, open, long term clinical investigation evaluating safety, performance and Patient Reported Outcomes (PRO) with the Osia 2 System in adult subjects 18 years or older with conductive hearing loss, mixed hearing loss or single-sided sensorineural deafness.

The subjects are the participants who performed the 3- and/or 6-month visit in the completed CBAS5751 investigation. The maximum number of subjects will be 27 from three clinics. The subjects will be followed at two visits, 12 and 24 months after the surgery date in the CBAS5751 investigation. The visit window at the 12-month visit will be opened as much as ± 5 months. The reason for this is to enable for as many subjects as possible to be included. At the time of investigation start the seven first implanted subjects in the CBAS5751 investigation have already passed their 12-month timepoint by several months. The performance of the device is not expected to change over this time period, but if it does, it will still be captured. This approach also provides the opportunity to collect safety data from the first seven subjects. At the final and most important time point 24 months, the visit window will be narrowed to ± 4 weeks.

The subjects will attend two scheduled investigation visits over a 12-month investigation period to be assessed as described in the Schedule of Events (Section 3). At investigation visits, subjects will be evaluated through objective audiological hearing tests, patient reported outcomes, questionnaires and safety assessments. The overall outcomes are to determine the hearing performance of the Investigational device at 12 and 24 months post-surgery and compare it with the last performed measurement (3 or 6 months) in the clinical investigation CBAS5751, assessed by sound-field thresholds audiometry, [PTA4, Mean of 0.5, 1, 2 and 4 kHz] and individual frequencies [0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0 and 8.0 kHz] and Adaptive speech recognition in noise. The self-reported outcomes will also be followed-up and compared with previous reported values. Safety will be assessed by recording and summarising all AEs/ADEs and DDs. A compilation of all AEs and DDs will be performed after all subjects have completed their 12-months visit. A full clinical investigation report will be prepared after the 24-month statistical analysis has been performed.

No data monitoring committee will be used for this clinical investigation.

7.1.1 Design Rationale

The rational for the design of this investigation is the intention to collect long-term safety and performance Osia 2 system data to meet expected requirements from any Notified Body or Regulatory agency. Following subjects from the previous CBAS5751 clinical investigation is judged

as a fast and efficient way to collect such data, since these subjects are already implanted with the Osia 2 system. To be able to compare performance and safety of the device over time similar endpoints as in the previous investigation will be chosen. In addition, the subjects will be asked questions regarding device satisfaction, sound satisfaction, usability and health care utilisation to collect information for current and future comparison with other studies.

The audiometric thresholds (pure tone average PTA4 and individual frequencies) and speech recognition in noise measured in sound-field, are relevant and objective methods that are commonly used by clinics internationally as a way to assess hearing performance, and they were both used in the CBAS5751 investigation.

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 simulate 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 (7). The Chinese Hearing in Noise Test (CHINT) to be used in this clinical investigation was developed using the same rationale as the English HINT and has shown to be comparable, allowing the two tests to be compared directly across languages (8). 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 (9). It 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.

Questionnaires to collect patient reported outcomes—Abbreviated Profile of Hearing Aid Benefit (APHAB) (10) and Speech, Spatial and Qualities of Hearing Scale (SSQ) (11) and the health related quality questionnaire, HUI (12) are well established methods that are abundantly referred to in the scientific literature. All three tests questionnaires were used in the CBAS5751 investigation.

From a health economic perspective, HUI and an adapted version of the Client Service Receipt Inventory (CSRI) will be used. HUI will collect information on how the different quality of life aspects change over time. Do the initial improvements remain the same, and do some improvements decrease as a result of ageing or disease?

CSRI is a research instrument developed to collect socio-economic information on service utilisation, income, accommodation and other cost-related variables (13). Its primary purpose is to allow resource use patterns to be described and support costs to be estimated using an appropriate unit cost. It has been used in over 500 studies according to PSSRU (Personal Social Service Research Unit).

7.2 Subjects

Written informed consent must be obtained before any investigation procedures are initiated.

7.2.1 Inclusion Criteria

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

1. Subject has performed Hearing assessment at 3 and/or 6 months in the clinical investigation CBAS5751
2. 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. 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
2. Use of ototoxic drugs that could be harmful to the hearing, as judged by the investigator

7.2.3 Number of Subjects Required

The subjects are participants who have performed the 3- and/or 6-month visit in the completed Osia clinical investigation CBAS5751. The maximum number of subjects will be 27.

7.2.4 Vulnerable Populations

Not applicable

7.2.5 Recruitment & Investigation Duration

The following subject status definitions apply:

- 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.

The enrolment period for the clinical investigation is anticipated to be four months from the time of first subject consent to enrolment of the last subject.

The expected duration of each subject's participation in the clinical investigation, is 12 months, from the time of informed consent through to the End of Investigation visit 12 months after visit 1.

Clinical Investigation completion is last subject last visit. The anticipated total duration of the clinical investigation is 17 months, including visit windows and follow-up time in the event of an ongoing SAEs/SADEs at the time of this last visit. Ongoing SAEs/SADEs will extend the clinical investigation completion 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 the reason(s). The reason for withdrawal should to be documented in the subject's source files and the case report form (CRF).

The Investigator or Sponsor may also decide to withdraw a subject from the clinical investigation if it is considered to be in their best interest.

Subject withdrawal may be for any of the following reasons:

- Adverse Event (AE)
- Device Deficiency (DD)
- CIP or GCP deviation
- Subject lost to follow-up
- Subject withdrew consent
- Subject death
- Sponsor decision
- Investigator decision

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 End-of-Investigation visit.

If a subject is lost to follow-up, every possible effort must be made by the investigation site personnel to contact the subject and determine the reason for discontinuation. At least 3 separate attempts taken to contact the subject must be documented.

Enrolled subjects who are withdrawn/discontinued will not be replaced.

7.2.7 Randomisation Procedures

Not applicable

7.2.7.1 Blinding Procedures

Not applicable

7.2.8 Post-investigation Medical Care

After the clinical investigation 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 Demographics

The following demographic data will be collected from the previous CBAS5751 investigation:

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

7.3.2 Post-Enrolment Evaluations and Procedures

7.3.2.1 Audiometry testing

If the study team experience an "unreasonable value" in any test, the test should be performed again after a short while to confirm validity.

7.3.2.1.1 Audiogram

To follow how the subject's hearing thresholds change over time, unaided audiometric threshold measures (including both air- and bone conduction thresholds) will be recorded at 12 and 24 months and compared with the same data collected at baseline before implantation in the CBAS5751 investigation.

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.

7.3.2.1.2 General instructions for audiological assessments

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

All tests shall be performed in a sound insulated room. Equipment used for audiological testing shall be calibrated according to the clinic's normal standard before initiation of the investigation. The speakers should be at the height of the test subject's head and more than 1 meter away from the test subject. There should preferably be more than 1 meter of free space around the test subject in all directions. This is in accordance with the current standard (14). It is important to keep the same sound room and test equipment set-up during the entire clinical investigation. ***Changes may be necessary and allowed, but only after approval by the Sponsor.***

7.3.2.1.2.1 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 sound-field measurement on PTA4 frequencies (500, 1000, 2000, 4000 Hz) shall be performed. The blocking shall then be done with earplug and muff and an additional sound-field measurement on PTA4 frequencies shall then be performed to verify effective blockage and document the hearing level after blockage.

7.3.2.1.2.2 Settings for the Sound Processors

The Investigational device should be tested using the Everyday program, with active gain disabled.

7.3.2.1.3 Audiological assessments

7.3.2.1.3.1 Sound Processor fitting

OFS (version 2) will be used to adjust the Investigational device settings for a specific subject. This will be performed during fitting at the 12- and 24-month visit and at an extra visit if 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 investigation 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 investigation. This will also provide an indication of the soft tissue thickness during the course of the investigation.

7.3.2.1.3.2 Bone Conduction (BC) Direct

BC Direct is a tool in the OFS (current version) to establish the unmasked bone conduction threshold with tones presented through the sound processor. BC Direct measurements (as part of the OFS) will be performed at 12 and 24 months 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.

7.3.2.1.3.3 Sound-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 3). 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.

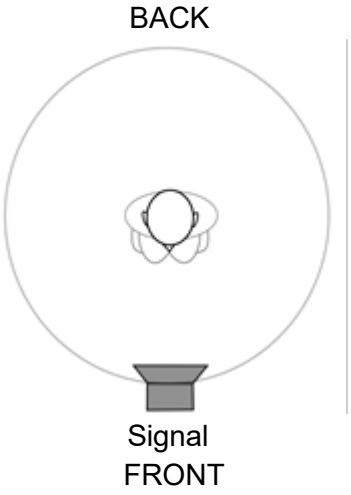

Figure 3: The setup of the speaker when testing sound-field thresholds.

7.3.2.1.3.4 Speech test

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 sound field from the front speaker (0 degrees azimuth, S_0N_0) (Figure 4). In Hong Kong software and speech material to be used is the CHINT (8), 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 (9), where 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.

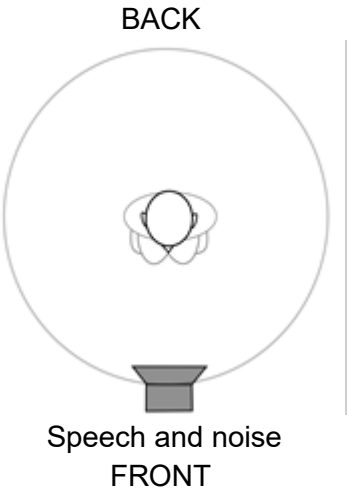

Figure 4. The setup of the speakers when testing Adaptive Speech recognition in noise.

This measurement shall be performed with the Investigational device at 12 and 24 months.

7.3.2.1.3.5 Cochlear Device Image (CDI) tool

The CDI tool is an engineering software used to establish the unmasked bone conduction high frequency thresholds with tones presented through the sound processor. The CDI measurements will be performed at 12 and 24 months when the subject is using the Investigational device. The CDI thresholds obtained at the following frequencies will be recorded; 6, 7, 8, 9 and 9.5 kHz.

7.3.2.2 Patient reported outcomes

7.3.2.2.1 Abbreviated Profile of Hearing Aid Benefit (APHAB form A)

The APHAB form "A" questionnaire (10) 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 12 and 24 months follow up for the aided situation (with the Investigational device).

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

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

The short form of Speech, Spatial, and Qualities of Hearing Scale questionnaire (SSQ-12) (15) from MRC Institute of Hearing Research, UK, is a scaled-down version of the 49 items SSQ questionnaire (11). 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 (15). 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 the 12- and 24-months follow-up for the aided situation (with the Investigational device).

The SSQ-12 questionnaire is free for use, confirmed by [redacted], former Director of MRC Institute of Hearing Research, which closed down 2018.

7.3.2.2.3 Health Utilities Index (HUI)

HUI® (12) 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 investigation (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 (12). The version in this clinical investigation uses a recall time of 1 week.

The subjects will complete the HUI at the 12- and 24-months follow-up 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.

7.3.2.2.4 Questions regarding the satisfaction with the device

At 12 and 24 months the subjects shall estimate the experience of the SP in relation to every-day situation, self-esteem, the easiness to use, durability of the device and sound quality using a Likert scale. It is a five- or seven-point scale which allows the individual to express how much they agree or disagree with a particular statement. The subjects shall also state if they are overall satisfied with the device, by answering yes or no.

7.3.2.3 Usability

7.3.2.3.1 Daily use

At the 12- and 24-months visit, data regarding daily use of the sound processor will be collected.

The estimated average hours of daily use (hours/day) during the last week before each follow up visit shall be recorded.

7.3.2.3.2 Daily streaming

At the 12- and 24-months visit, data regarding daily streaming using the sound processor shall be collected. Streaming of for example phone calls or music, can be done directly from an iOS or Android phone, or by using the wireless accessories.

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

7.3.2.3.3 Battery lifetime

At the 12- and 24-months 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.

7.3.2.3.4 Magnet choice

There are 4 different magnet strengths, ranging from 1 to 4, strength 1 being the weakest. At the 12- and 24-months visit, 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.

7.3.2.3.5 SoftWear Pad use

At the 12- and 24-months visit, data regarding SoftWear pad use (Yes/No) for the sound processor will be collected.

7.3.2.3.6 Sound Processor retention

At the 12- and 24-months visit, 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.

Insufficient retention	*Excellent retention*

7.3.2.3.7 Sound Processor wearing comfort

At the 12- and 24-months visit, 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*

7.3.2.4 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 investigation 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 8.2 of the CIP, will be assessed in the clinical investigation 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.
When all 12 months visits have been performed an interim safety evaluation will be performed

regarding all AEs and DDs reported. This evaluation will be performed by the team responsible for the clinical investigation, including the Safety contact/monitor. The interim safety evaluation will be documented in a report.

7.4.1 Concomitant Medication and Therapies

Relevant Medications and treatments, as judged by the Investigator, that are given to the subjects should be entered in the eCRF.

Prohibited therapies are the following:

- ototoxic drugs

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

7.4.2 Client Service Receipt Inventory (CSRI)

CSRI is a research instrument developed to collect socio-economic information on service utilisation, income, accommodation and other cost-related variables (13). Its primary purpose is to allow resource use patterns to be described and support costs to be estimated using an appropriate unit cost. It is free to use and allows users to exclude questions not relevant for the investigation in which it is to be used.

The adapted version of CSRI will, in this investigation, collect data referent to the 12 months before each visit regarding demographics (marital status, cohabitation, usual place of residence, education level), employment status and healthcare utilisation and hearing rehabilitation.

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.

The OFS and CDI tool together with a user manual or work instruction for the software according to current released version 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 were checked and approved by the Sponsor at the previous CBAS5751 investigation. Equipment used for audiological testing shall be calibrated according to the clinic's normal standard before initiation of the investigation. Calibration certificates will be asked for by the Sponsor as part of the investigation documentation.

If needed, technical expertise will be provided in the study, for example for installation of programming software, provision of training on the software or troubleshooting with the performance of integrity tests.

8 RISKS AND BENEFITS OF THE INVESTIGATIONAL MEDICAL DEVICE AND CLINICAL INVESTIGATION

8.1 Anticipated Clinical Benefits

Most recipients of a bone conduction hearing solution will experience an improved hearing performance and quality of life compared to unaided listening.

Compared to treatment according to standard practice at the clinic, the participants in this investigation will be more closely monitored regarding the IMD and also get the opportunity to meet and interact more with the audiology team and other medical staff at the clinic. The participation will lead to better knowledge on long term performance and safety which might be beneficial for future Osia System Recipients.

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, the subjects were implanted and provided with the Osia 2 System in the previous prospective, multicentre clinical investigation CBAS5751 where safety and performance of the Osia 2 System were tested in short term, at 3 and 6 months.

The CBAS5751 clinical investigation on the Osia 2 System showed no serious adverse events or device deficiencies related to the Implant (OSI200).

The following adverse device effects were reported in relation to the procedure; infected wound (6), muscular neck pain in region inferior to operation site (2), pain (1), ear pain (1), crust on wound (1) and hair follicle caught in wound (1).

In addition, the following adverse device effects related to the device or both the device and the procedure have been reported (to date). Pain at implant site (4), itchiness and discomfort around incision (4), infection (1), tender skin at sound processor site (1), increased tinnitus (1), discomfort due to sound processor heating up (1), prominence of the edge of the Osia implant (1), distress (1) and frustration (1). In the CBAS5751 clinical investigation numbness was evaluated separately, not reported as an AE. Around 50% of the subjects reported numbness in the implant area during the investigation.

In a clinical investigation with the first generation Osia implant and Osia Sound Processor (16) the same kind of adverse device effects were reported. In addition, headache, vertigo, neuropathic pain and three cases of warm skin when using the device were reported. The issues were transient and did not cause any suffering to the subjects. In a clinical investigation with the first generation Osia implant, but the current Osia Sound Processor (17) one adverse device event was reported; skin irritation under the SP which was resolved after a few days of not using the device and adding a SoftWear pad.

More information and details with regards to any risks with the use of the Investigational device is provided in the Investigator´s Brochures (3) (4).

8.3 Risks Associated with Participation in the Clinical Investigation

The subjects are already implanted with the investigational device and using the Sound Processor, no additional risk is therefor expected for participation. The long-term risk of using the Osia System is unknown, which will be followed in this investigation in a controlled way until 24 months post implantation.

Due to the current COVID-19 pandemic it could be a potential risk for the subjects to visit the clinics in case of increased outbreaks in the respective regions.

8.4 Risk Mitigation

All reported ADEs and DDs will be reviewed regularly by the Sponsor for the duration of the clinical investigation to facilitate early detection and appropriate intervention if events are unanticipated with respect to incidence, severity, or outcome.

Respective clinic will handle the Covid-19 situation according to local regulations and instructions.

8.5 Risk-to-Benefit Rationale

The long-term risks using this Osia 2 System is still unknown. In relation to the individual benefit to be more closely monitored regarding the IMD and also get the opportunity to meet and interact more with the audiology team and other medical staff at the clinics the benefits are considered to overweight the risks. Participation in this clinical investigation could lead to increased risk for the subject to be infected by COVID-19 when visiting the clinic but is judged as limited as long as the subjects and clinics follow local regulations.

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. Mean changes over time will be presented along with 95% CI.

All data will be presented in summarized tables and figures along with listings of individual data. The last non-missing measurement from the CBAS5751 investigation (3- and 6-months visits) will serve as the baseline reference in this follow up analysis for each subject. Changes from this baseline measurement will be evaluated statistically using a paired statistical methodology, each subject serves as his/her own control. Data collected at 12 and 24 months will be presented by visit where applicable. Data which are of collected continuously over time such as Adverse event and Device deficiency will be presented as Number of events and Number of subjects with events, and not by visits. Efficacy audiology measurements will be compared to the subjectively evaluation of the satisfaction with the system in order to find out if there are any useful clinical audiological cut-offs where a subject is satisfied or not.

Analyses at 12 months will be based on subjects attending the 12 months visit and analyses at 24 months analyses will be based on subjects attending the 24 months visit. No per protocol analyses will be performed and no imputation of missing data will be made.

Pass/fail criteria to be applied to the results:

- The objective is considered as fail if more than two of the subjects have experienced a related serious adverse event with the same root cause within the first 24 months from surgery.
- The objective is considered as fail if more than two of the subjects have an increase in PTA-4 Sound field threshold >15 dB at 24 months compared to the last obtained aided PTA value in CBAS5751 (3 or 6 months).
- The objective is considered as fail if more than two of the subjects have an increase in SNR field threshold >1 unit at 24 months compared to the last obtained aided SNR value in CBAS5751 (3 or 6 months).

If a failed result regarding PTA-4 or SNR is obtained a root cause analysis will be performed to confirm that the failed value depends on declined performance and not on other factors such as impaired unaided hearing, incorrectly performed tests or other causes.

If any of the criteria are failed the investigation is considered as fail.

No formal hypothesis testing will be performed in this long term follow up study.

No termination of the study will be made on statistical grounds.

Protocol deviations will be listed in listing appendix.

No Statistical Analysis Plan (SAP) is planned to be produced.

9.2 Endpoints

9.2.1 Safety Endpoints

- Adverse events (including explantations, revision surgery)
    - AEs,
    - ADEs,
    - SAEs,
    - SADEs and
    - AESIs.
- Device deficiencies
- Use of concomitant medication
- Compare baseline audiogram before implantation with audiogram at follow up visits to investigate if the thresholds have been constant over time. Bone- and air conduction thresholds, masked and unmasked, at 12 and 24 months.
- Socio-economic health care data will be collected at 12- and 24 months. It will be estimated and used at a later stage together with data from other sources.
    - Demographics: marital status, cohabitation, usual place of residence, education level
    - Employment status
    - Healthcare utilisation

- Hearing rehabilitation

9.2.2 Performance Endpoints

- The hearing performance at 12- and 24-months post-surgery when using the Investigational device compared to the hearing performance at of 3- and 6-months in the CBAS5751 investigation assessed as:
  - The change in Thresholds audiometry, sound-field [PTA4, mean of 0.5, 1, 2 and 4 kHz]
  - The change in Thresholds audiometry, sound-field [0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0 and 8.0 kHz].
  - The change in Adaptive speech in noise [signal-to-noise ratio, 50% speech understanding].
- 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 the Investigational device at 12- and 24-months post-surgery.

9.2.3 Patient Reported Endpoints

- The benefit in self-reported hearing outcome when using the Investigational device at 12- and 24-months post-surgery compared with the benefit at 3- and 6-months post-surgery in the CBAS5751 investigation assessed by:
  - The change in scores using the Abbreviated Profile of Hearing Aid Benefit (APHAB).
  - The change in scores using the Speech, Spatial and Qualities of Hearing Scale (SSQ).
- The benefit in health-related quality of life (HRQoL) when using the Investigational device at 12- and 24-months post-surgery compared with the benefit at 3- and 6-months post-surgery in the CBAS5751 investigation.
- Usage information at 12 and 24 months:
  - Magnet choice
  - Sound Processor retention
  - Sound Processor wearing comfort
  - Use of SoftWear pad
  - Daily use
  - Daily streaming
  - Battery lifetime
  - Retention
  - Comfort
- Subjective questions at 12 and 24 months:
  - Every-day situation
  - Self-esteem
  - Sound quality

- Easy to use
- Durability
- Overall satisfaction (Yes/No)

9.2.4 Exploratory Endpoint

- High frequency thresholds [6.0, 7.0, 8.0, 9.0 and 9.5 kHz] will be collected with the CDI tool, using the Investigational device at 12- and 24-months post-surgery.

9.3 Hypotheses

No hypothesis testing will be made in the study. Confidence limits and p-values presented in the analyses are considered to be exploratory.

9.4 Sample Size Determination

This is a long term follow up study of the CBAS5751 study and no specific sample size calculation will be made here.

9.5 Analysis Populations

Subjects attending the 3- and/or the 6-months visit in the original CBAS5751 study who accept to participate in this long term follow up *investigation* and attends the 12- or 24 months visit will be analysed. No per protocol population will be defined.

9.6 Safety Endpoint Analyses

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). Number of events, number of subjects and percent of subjects with events will be presented by System Organ Class (SOC) and term in the CTCAE or IMDRF. Which system to be used will be decided and documented before the database is locked

Device deficiency will be summarized and presented as number and percentage. Device deficiencies will be presented totally and by relationship (Sound Processor, Implant, OFS or Accessories).

Concomitant medications will be presented in patient individual listings.

Descriptives for the socio-economic data, demographics and information on service utilisation related to hearing rehabilitation will be summarized for all patients.

9.7 Performance Endpoint Analyses

All performance variables will be presented by visit and changes where applicable according to paragraph 9.1. Wilcoxon signed rank test will be performed for changes in continuous variables over time, for changes in dichotomous outcomes Sign test will be used to evaluate better/equal/worse.

Analyses of PTA-4 thresholds and SNR vs overall satisfaction at 24 months will be made in order to find if there is any cut off point on these variables which predicts if a patient is satisfied or not. This will be made using logistic regression and c, ROC-curve and effect plot of predicted probability by PTA-4 and SNR will be presented.

9.8 Patient Reported Outcomes Endpoint Analyses

All patient recorded variables will be presented by visit and changes where applicable according to paragraph 9.1. Wilcoxon signed rank test will be performed for changes in continuous variables over time, for changes in dichotomous outcomes Sign test will be used to evaluate better/equal/worse.

9.9 Exploratory Endpoint Analyses

High frequency thresholds [at 6.0, 7.0, 8.0, 9.0 and 9.5 kHz] will be presented by visit, both individual and mean values.

9.10 Interim Analyses

An interim safety analysis will be performed when all subjects have completed their 12-months visit. A compilation of all AEs and DDs that occurred between the 6-months visit in CBAS5751 and the 12-months visit in this investigation will be performed. In addition, follow-up of any unresolved AEs at the 6-month visit in CBAS5751 will be done.

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:

a) led to a death,

b) 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.

c) 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 Brochures (3) (4).

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.

11.1.6 Adverse Events of Special Interest

- 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 Device Deficiency (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 the last visit in the CBAS5751 investigation. 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 either IMDRF or CTCAE to System Organ Class (SOC) and IMDRF/CTCAE term. Decision will be taken in due time before database lock.

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 medical 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 8.2 of 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 investigation visits. 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

All DDs 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 and Sound Processors should be sent to CLTD.

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 a 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 a SADE, and AESI, must be reported to the Sponsor within 24 hours after awareness.

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 investigation, 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

Subjects in this investigation have been provided with the investigational device in the previous CBAS5751 investigation. In case of need of replacement of the sound processor the following procedure should be followed:

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

Supply of investigational devices will be recorded using the Sponsor Device Tracking Form (1295388) and Software Tracking Form (1302326). Investigational device(s) will be quarantined at the investigational site and clearly labelled to identify exclusively for use in a clinical investigation.

Subject level device supply will be tracked using the Sponsor's Individual Subject Accountability Log Form (1295295).

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

At the end of the clinical investigation, all unused medical devices shall be returned to the Sponsor.

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 the datapoints necessary to determine the subject status according to the criteria described in section 7.2.5.

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. Publications or submission to an EC shall not disclose the identity of any subject.

16 ETHICS COMMITTEE AND REGULATORY AUTHORITY 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 investigational plan, or the responsible regulatory authority.

Any additional requirements imposed by the EC 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 investigation. The Investigator will send written status summaries of the investigation to the EC regularly, as per local EC requirements.

Upon completion of the clinical investigation, 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.

Notification to Therapeutics Goods Administration (TGA) is needed in Australia before commencing the study.

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 until the IMD is approved by national regulatory authority.

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.

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 investigation-related records after completion of the investigation.

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 investigational site, the Sponsor should be notified of the name of the person who will assume responsibility for maintenance of the records at the investigational 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

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3. ***D1577642, Investigator's Brochure OSI200.***

4. ***D1503289, Investigator's Brochure Osia 2 SP.***

5. ***D1703580, CBAS5751 Clinical Investigation Report.***

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8. Wong LL, Soli SD. ***Development of the Cantonese Hearing In Noise Test (CHINT). 3, 2005, Ear Hear., Vol. 26, ss. 276-89.***

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10. Cox RM, Alexander GC. ***The abbreviated profile of hearing aid benefit. 2, Apr 1995, Ear Hear, Vol. 16, ss. 176-86.***

11. Gatehouse S, Noble W. ***The Speech, Spatial and Qualities of Hearing Scale (SSQ). 2 Feb 2004, Int J Audiol, Vol. 43, ss. 85-99.***

12. Feeny, David, William Furlong, Michael Boyle, and George W. Torrance. ***Multi-Attribute Health Status Classification Systems: Health Utilities Index, 6, June 1995, PharmacoEconomics, Vol. 7, ss. 490-502. pp. 490-502.***

13. Beecham J, Knapp M. ***Costing Psychiatric Interventions. In Thornicroft G, Brewin CR, Wing J. Measuring Mental Health Needs. London: Gaskell; 1992. pp. 163–183.***

14. ***ISO 8253-1 2010, Acoustics - Audiometric test methods - Part 1: Pure-tone air and bone conduction audiometry.***

15. Noble W, Jensen NS, Naylor G, Bhullar N, Akeroyd MA. ***A short form of the Speech, Spatial and Qualities of Hearing scale suitable for clinical use: the SSQ12, 6 2013, International Journ.of Audiol, Vol. 52, pp. 409-12.***

16. ***D1478473, CLINICAL INVESTIGATION REPORT, Clinical performance of a new implant system for bone conducting hearing. 2019.***

17. ***D1635125, CLINICAL INVESTIGATION REPORT, Subject's preference regarding hearing performance and functionality using a new sound processor, 2019.***

25 CHANGE HISTORY

Version	Change	Rationale
2	• HINT Hearing in Noise test was included in section 7.1.1. and 7.3.2. • Safety data updated with 6 months results from the CBAS5751 study in section 4.2.2. and 8.2. • Minor corrections and clarifications.	• This Hearing in Noise test is to be used at the Hong Kong site. Information about the test was missing in the previous version. • 6 months safety results from CBAS5751 were analysed and completed between version 1 of the CP and this version 2 CIP.
3	• 7.4.1: Updated specification of which concomitant medications and treatments should be entered in the CRF. • Signature page Hong Kong: Site name corrected.	• We are only interested in medications and treatments for adverse events that may be related to the investigational device. • Incorrect site name.