Clinical Investigation Plan (CIP)

Investigation code	CBAS5731
Version	3 Final
Version date	11 December 2018

Subject´s preference regarding hearing performance and functionality using a new sound processor

Single-center, prospective, open within-subject comparison with randomised device test order.

This CIP version 3 includes the following addition:

CIP version	Date	Comments
2	02 October 2018	Original submitted to HREC
3	11 December 2018	A section regarding Safety assessment added after request by HREC.

NCT03848910

SYNOPSIS

Name of sponsor	Cochlear Bone Anchored Solutions AB
Investigation code	CBAS5731
Investigational title	Subject´s preference regarding hearing performance and functionality using a new sound processor
Design	Single-centre, prospective, open, within-subject comparison with randomised device test order.
Investigational device(s)	Osia ® 2 Sound Processor (Osia 2 SP)
Comparator(s)	Osia Sound Processor (Osia SP)
Aim for conducting the investigation	To investigate test-subject overall preference, hearing performance and self-reported assessments with Osia 2 SP and Osia SP.
Inclusion criteria	• Completed clinical investigation CBAS5539, and an active user of the Osia System. • Signed Informed Consent. • Subject with conductive or mixed hearing loss in the implanted ear. Bone conduction thresholds with pure tone average (PTA4; mean of 0.5, 1, 2 and 4 kHz) of ≤ 55 dB. OR Subject with single-sided sensorineural deafness. Air conduction thresholds with a pure tone average PTA4 of ≤ 20 dB HL (mean of 0.5, 1, 2 and 3 kHz) in the good ear. • Optimally fitted with Osia SP, according to subject's experience prior to inclusion.
Exclusion criteria	• Any ongoing soft tissue complication that could affect the use of the Osia 2 SP during the study period. • Use of ototoxic drugs that could be harmful to the hearing, as judged by the investigator. • Unable to follow investigational procedures and instructions, e.g. inability to complete quality of life scales or audiological testing as described in this CIP. • Participation in another clinical investigation with pharmaceutical and/or device.
Number of subjects	Up to 12
Duration of subjects participation	6 weeks in total

Overall objective	Measurements
To compare the subject's overall preference between the Osia 2 SP and Osia SP	• Preferred choice made by selection between Osia 2 SP and Osia SP • Self-reported assessments ➢ Abbreviated Profile of Hearing Aid Benefit (APHAB) ➢ Speech, Spatial, and Qualities of Hearing Scale (SSQ) ➢ Self-reported assessment regarding satisfaction and usability (QUEST version 2) • Audiometric thresholds in free field ➢ Thresholds audiometry, free-field [PTA4, Mean of 0.5, 1, 2 and 4 kHz]. ➢ Thresholds audiometry, free-field [0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0 and 8.0 kHz]. • Speech recognition tests in quiet and noise ➢ Adaptive speech in noise [speech-to-noise ratio, 50% speech understanding]. ➢ Speech in quiet [% correctly perceived words at 50dB, 65dB and 80dB SPL].
To assess the subject's experience regarding Comfort and specific usage	• Subjective experience regarding Comfort and specific usage ➢ Comfort ➢ Magnet choice ➢ Battery life ➢ SoftWear pad use ➢ Safety line use ➢ Wireless accessories and iPhone connectivity

Safety objective(s)	Outcome measure(s)
Adverse Events and concomitant	Information will be collected from Visit 1

medication/treatment	
Device deficiency	Information will be collected from Visit 1

Procedures and timing	Visit 1	Visit 2/ Contact *	Visit 3
Day/Week/Month	Day 0	14 days	6 weeks
Time window		± 5 days	± 5 days
Demographics	X		
Medical history	X		
Eligibility criteria	X		
Audiogram	X		
Baseline characteristics	X		
Informed consent	X		
Sound Processor Fitting			
Magnet choice	X[1]	X[3]	
Digital link calibration (DLC)	X[1]	X[3]	
Feedback measurement	X[1]	X[3]	
BC Direct	X[1]	X[3]	
Fine tuning[1]	X[1]	X[3]	
Randomised device test order			X
Thresholds audiometry, free-field			X
Speech recognition in noise			X
Speech recognition in quiet			X
APHAB	X[2]		X[1]
SSQ	X[2]		X[1]
QUEST	X[2]		X[1]
Comfort and Specific usage: Comfort, magnet choice, battery life, SoftWear pad, Safety line	X[2]		X[1]
Wireless accessories			X[1]
Subject´s overall preference			X[4]
Adverse events	X	X	X
Device deficiency	X	X	X
Concomitant treatment	X	X	X
Extra visit			

*Visit 2 is optional as a Visit. Can be done by contact via phone call

[1] Investigational device

[2] With Comparator

[3] As required, Investigational device

[4] Investigational Device vs Comparator

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Appendix	Title
NA	NA

ABBREVIATIONS

ADE	Adverse Device Effect
AE	Adverse Event
AESI	Adverse Event of Special Interest
APHAB	Abbreviated Profile of Hearing Aid Benefit
Baha	Bone anchored hearing device
BC	Bone Conduction
CBAS	Cochlear Bone Anchored Solutions AB
CE	Conformité Européenne
CHL	Conductive Hearing Loss
CIP	Clinical Investigation Plan
CRF	Case Report Form
DCL	Digital link calibration
FDA	Food and Drug Administration
ISO	International Organization for Standardization
ICMJE	International Committee of Medical Journal Editors
LED	Light Emitting Diodes
MHL	Mixed Hearing Loss
OFS	Osia Fitting Software
QUEST	Quebec User Evaluation of Satisfaction with assistive Technology
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SNHL	Sensorineural Hearing Loss
SP	Sound Processor
SSD	Single Sided sensorineural Deafness
SSQ	Speech Spatial and Qualities of Hearing Scale
TGA	Therapeutic Goods Administration
US	United States
USADE	Unanticipated Serious Adverse Device Effect

1 INTRODUCTION

1.1 Background

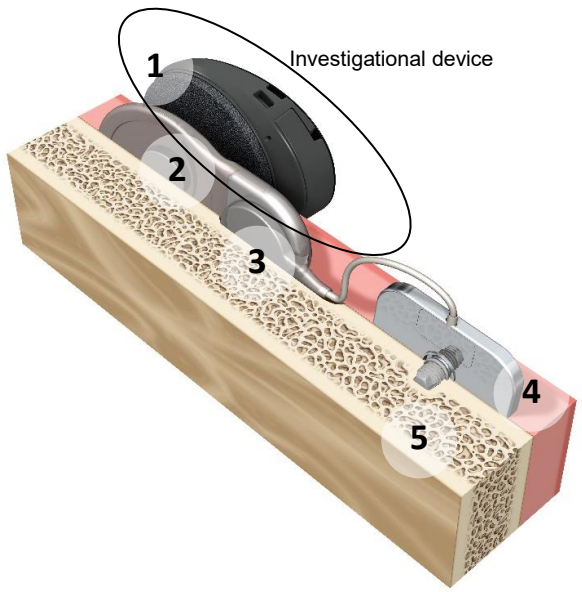
1.1.1 The Osia system

The Investigational device, the Osia ® 2 Sound Processor, is part of the Osia ® System, which is an active implantable bone conduction hearing system intended to compensate for conductive hearing loss (CHL), mixed hearing loss (MHL), or single-sided sensorineural deafness (SSD) by transmitting amplified acoustic signals to the cochlea through mechanical vibration of the skull bone.

The Osia System consists of an internal and an external part (figure 1). The internal part is the implant consisting of a receiver/stimulator and an actuator (vibrator) which is surgically implanted on the temporal bone and attached to an osseointegrated titanium fixture (BI300 Implant). The external part is a sound processor, an off-the-ear button processor, which picks up the sound from the environment and sends the information, after processing, to the implant via an inductive radio frequency link. Each system is configured to meet an individual's impaired hearing needs by using a dedicated fitting software, the Osia Fitting Software.

The actuator converts the electrical signal into an amplified mechanical stimulation and transmits it to the mastoid bone through the osseointegrated BI300 implant, bypassing the impaired middle ear (origin of the conductive part of the hearing loss) and optionally providing mechanical amplification in order to compensate for the damaged hair cells (sensorineural part of the hearing loss, in case of mixed hearing loss). For SSD subjects the amplified mechanical stimulation is transferred though bone conduction to the contralateral functioning cochlear.

Figure 1. Overview of the Osia System



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 receiver-stimulator converts the digital information into an electric analogue signal.
4. This electric signal is converted to vibrations by the implant piezoelectric actuator.
5. The vibrations are transmitted to the skull bone through the BI300 Implant, and onwards to the cochlea.

The Osia System is indicated for people with uni- or bilateral conductive or mixed hearing loss and for people with single-sided sensorineural deafness (SSD). It is indicated for adult recipients, with a fitting range of up to 55 dB SNHL (for mixed hearing loss).

The Osia System with the second generation sound process—the Osia 2 Sound Processor—combines favourable aesthetics with improved features (Wireless, Noise reduction and Active Gain) compared to the first generation Osia Sound Processor. The sound processor is worn on the skin over the implant site on a daily basis for up to a full day.

1.2 Aim of the clinical investigation

The aim of this clinical investigation is to investigate the subject´s overall preference, hearing performance and self-reported assessments with the Osia 2 Sound Processor (Investigational device) and the Osia Sound Processor (Comparator) after 6 weeks in subjects with conductive/mixed hearing loss or SSD.

2 MEDICAL DEVICE(S) USED DURING AND AFTER THE INVESTIGATION

2.1 Investigational device and comparator

2.1.1 Description of the Investigational device

The Osia 2 Sound Processor (Osia 2 SP) is a button-type, second generation sound processor to be used with an OSI100 Implant already implanted and in use by the subjects taking part in the clinical investigation. The Osia 2 SP offers an improvement over the previous generation sound processor (Osia SP) with regards to size (figure 2), weight, signal processing and wireless functionality (see table 1*)*.

Figure 2. The Osia ® 2 Sound Processor views and size.

During use, the Osia 2 SP is, like the first generation Osia SP, in contact with the skin or hair and is kept in place by two magnets, one magnet in the Osia 2 SP and one implanted magnet in the OSI100 Implant (Figure 3). The intended use is daily and as long as the subjects feels they need to have amplification, which could mean a full day.

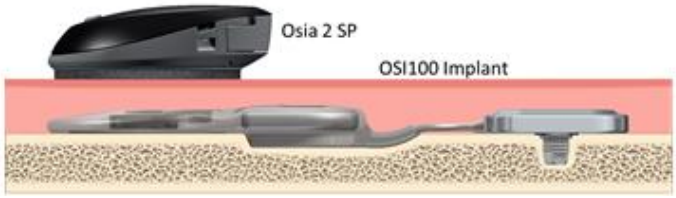
Table 1. The Osia ® 2 Sound Processor features

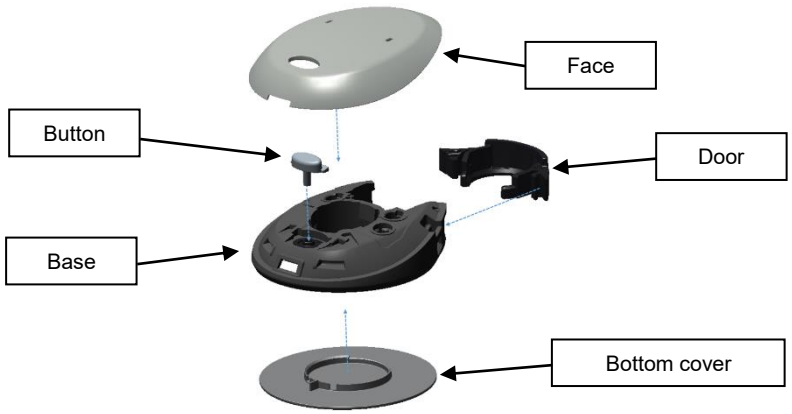
Feature	Osia 2 SP
Material Processor unit	Polyamide
Weight (with battery and magnet 4)	11,6 g
Battery	One PR44
Compatible implant	OSI100 Implant
Digital sound processing	NEOXS and Lacerta C4.5
Wireless Accessories	As specified in 2.3.2

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

The Osia 2 SP is powered by one battery which is expected to be enough for one full day of use.

Figure 3. Osia System: Top. Osia 2 Sound Processor with the OSI100 Implant. Below: partially exploded view.





In normal operation, the Osia 2 SP and OSI100 Implant function as follows:

- The sound is picked up by the microphone in the sound processor and is digitally processed.
- The sound processor transmits the digital information and power to the implant.
- The implant receiver-stimulator converts the digital information into an electric analog signal.
- This electric signal is converted to vibrations by the implant piezoelectric actuator
- The Actuator is attached to the fixture, BI300 Implant, which transfers the vibrations into and through the scull bone to the Cochlea.

2.1.1.1 Manufacturer of investigational device(s)

The Osia 2 SP, magnets and packaging case are sourced and manufactured by Jabil Nypro in Shanghai China, outsourced by the legal manufacturer Cochlear Limited, Sydney, Australia. The facility is ISO13485 certified (Medical devices - Quality management systems).

2.1.2 Description of Comparator

The Osia Sound Processor (Osia SP) is the SP currently being used by the subjects who can participate in this clinical investigation. It consists of an all-in-one off-the-ear button processor: processing unit with active coil, magnet (with seven possible strengths), and two battery cells. The Osia SP and the OSI100 implant are CE-marked, and constitute the first generation Osia System. The Osia SP unit also contains light emitting diodes (LED) and one command button, which allows the patient to control the processing unit (Figure 4). The mode of operation is the same as for the Osia 2 SP, described in section 2.1.1.

Features of the Osia SP is presented in table 2.

Figure 4.Osia Sound Processor. Upper left: external view (upper surface). Upper right: partially exploded view. Low left : size. Low Right: SP and Implant In Vivo

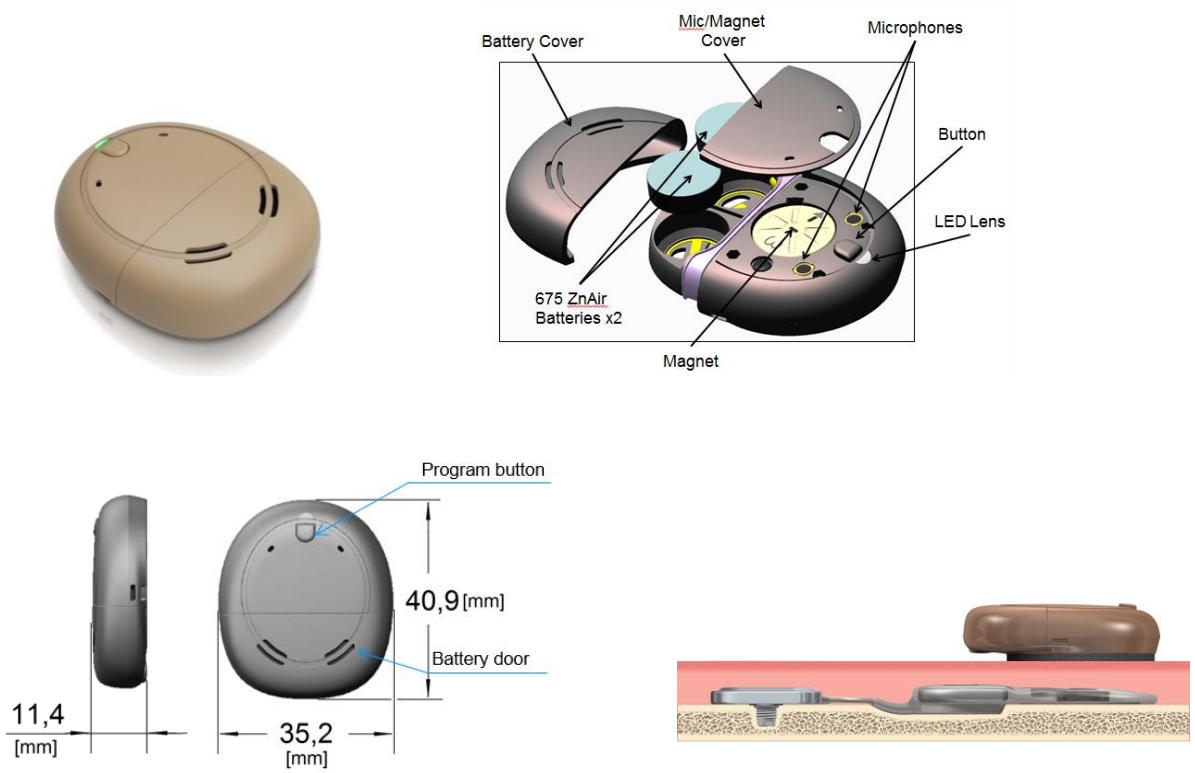


Table 2. The Osia Sound Processor features

Feature	Osia SP
Material Processor unit	Polyamide
Weight (with batteries and magnet 6)	18.7 g
Battery	Two 675 Zinc-Air batteries
Compatible implant	OSI100 Implant
Digital sound processing	NEO
Wireless Accessories	Not available

In this clinical investigation the Comparator will only be used in testing once, at Visit 3, to collect data to be compared with data from the Osia 2 SP.

2.1.2.1 Justification for the choice of comparator(s)

The Osia SP is the first generation Osia sound processors, and is CE marked. Cochlear Bone Anchored Solution AB´s internal testing and preliminary data from clinical investigation CBAS5539 [1] has shown that the Osia System works as intended and improves the subject's ability to hear. The intention from Cochlear is that the next generation sound processor, the Osia 2 SP, will provide at least as good hearing performance and be preferred by the

subjects that have the possibility to upgrade. Data collected from both SPs in this clinical investigation will be used to indicate this.

2.1.2.2 Manufacturer of comparator(s)

Cochlear Limited, Sydney, Australia.

2.2 Blinding

No blinding will be used in this clinical investigation.

2.3 Other device(s) used in the investigation

2.3.1 Osia Fitting Software

To adjust and fit the Osia 2 SP to each recipient a programming software will be used—the Osia Fitting Software (OFS) with the currently released version at the time of the clinical investigation. Communication between the computer-based software and the sound processor is achieved using a Hi-Pro 2 programming unit. This OFS to be used for the Osia 2 SP is built on and has comparable graphical user interface and features as the previous OFS 1.0 developed for the Osia SP, but with improved data logging and wireless capabilities/accessories which are the same as in the Baha Fitting Software (BFS 5.0).

2.3.2 Osia System accessories

Accessories which are approved and compatible with the Osia 2 SP will be available for use in the clinical investigation (free of charge for the subjects). The accessories are:

- Cochlear Wireless Phone-clip (ID 94773).
- Cochlear Baha Remote control 2 (ID 94793).
- Cochlear Wireless Mini-microphone 2+ (ID P770847).
- Cochlear Baha Safety line (ID P72062). Can be used to secure the Osia 2 SP in case of loss of magnetic retention.
- SoftWear pads (ID P793402).

2.3.2.1 Manufacturer of other non-investigational devices

For Wireless: Cochlear Bone Anchored Solutions AB, Mölnlycke, Sweden.

For Safety line and SoftWear pads: Cochlear Limited, Sydney, Australia.

2.4 Treatment after the completion of the investigation

After the clinical investigation the subjects will have the option to keep and continue to use their Osia 2 SP. Routine controls with audiological checks will follow local routines according to the standard treatment program for similar devices (e.g. active and non-skin penetrating, bone conduction hearing devices).

The Osia 2 SP will be warranted and supported with service according to normal Cochlear routines.

3 SUBJECTS AND SUBJECT PROTECTION

3.1 Selection of subjects

3.1.1 Inclusion criteria

A subject will be eligible for inclusion in the investigation if he/she meets **all** of the criteria below:

- Completed clinical investigation CBAS5539, and an active user of the Osia System.
- Signed Informed consent.
- Subject with conductive or mixed hearing loss in the implanted ear. Bone conduction thresholds with pure tone average (PTA4; mean of 0.5, 1, 2 and 4 kHz) of ≤ 55 dB.

  OR

  subject with single-sided sensorineural deafness. Air conduction thresholds with a pure tone average PTA4 of ≤ 20 dB HL (mean of 0.5, 1, 2 and 3 kHz) in the good ear.
- Optimally fitted with Osia Sound processor, according to subject's experience prior to inclusion.

3.1.2 Exclusion criteria

A subject will be excluded from participation in the investigation if he/she meets **any** of the criteria below:

- Any ongoing soft tissue complication that could significantly affect the use of the Osia 2 Sound Processor during the 6 weeks period
- Use of ototoxic drugs that could be harmful to the hearing, as judged by the investigator
- Unable to follow investigational procedures and instructions, e.g. inability to complete quality of life scales or audiological testing as described in this CIP.
- Participation in another clinical investigation with pharmaceutical and/or device.

3.1.3 Number of subjects

Up to 12 subjects will be included in the investigation.

3.1.4 Duration of subject participation

Subjects will participate during a 6 weeks period, involving up to 3 prescheduled visits.

3.2 Subject enrolment and Informed consent

Before a subject is asked to sign an informed consent form, the investigator must explain the following to the potential investigational subject:

- The rationale, aims and objectives of the investigation
- Any risks and benefits

- Alternative treatment solutions
- Extent of the subject's involvement
- He/she can withdraw his/her consent at any time
- The confidentiality of patient data will be maintained at all time
- The subject will be informed if new information becomes available that may be relevant to the subject's willingness to continue participation in the clinical investigation

The subject must have the opportunity to ask any questions. Signed and dated informed consent from potential subjects must be obtained before any investigational procedures can be performed. The enrolled subject will keep their subject number/Id number that was assigned to them in the previous completed CBAS5539 clinical investigation.

3.3 Randomisation

This is an open investigation. Randomisation will be performed for the device test order at Visit 3 (Osia 2 SP and Osia SP). See section 5.8.

3.4 Discontinuation

- Subjects are free to discontinue their participation in the investigation at any time
- Subjects may be discontinued from the investigation at any time at the discretion of the investigator
- Other reason for subject withdrawal or discontinuation is for example failure of OSI100 Implant function

Subjects who themselves discontinue from the investigation should always be asked about the reason(s) for the discontinuation and the presence of any adverse events. If possible, the subject should always be seen and assessed by an investigator. Any adverse event should be followed up.

3.5 Replacement of subjects

If a subject discontinues participation in the investigation, he/she will not be replaced.

3.6 Insurance

In case of any damage or injury occurring during the participation in the investigation, the Sponsor has contracted an insurance company, Chubb Insurance Australia Limited, which will cover the liability of the Sponsor, the investigators and other persons involved in the investigation. The Sponsor may use a local insurance company, where applicable, according to national legislation.

4 DESIGN OF THE CLINICAL INVESTIGATION

4.1 Design of the clinical investigation

This clinical investigation is an open, single-centre, prospective, within-subject comparison, with 2-3 visits over a period of 6 weeks. The data for the overall objectives will be collected at Visit 1 and at Visit 3. Subjects enrolled will all be previous participants in the CBAS5539 study conducted at the same clinic. No new implantations will be performed. A randomisation will be performed regarding the device test order at Visit 3 and each subject will be compared to his/her own questionnaire answers from Visit 1 and test results at Visit 3.

4.2 Justification for the design of the clinical investigation

The design consists of a within-subject comparison in terms of “preference”. The subjects are already using the Osia SP and comparisons will be made with the Osia 2 SP after 6 weeks of use. The sponsor is interested in gathering information regarding the user’s subjective everyday preference when using their own preferred settings.

Questionnaires to collect self-reported outcomes—Abbreviated Profile of Hearing Aid Benefit (APHAB) [2], Speech, Spatial and Qualities of Hearing Scale (SSQ) [3] and Quebec User Evaluation of Satisfaction with assistive Technology (QUEST) [4]—have been proven to be a helpful tools measuring changes in subjects benefits [5].

In addition to the subjective evaluations, thresholds audiometry in free-field (pure tone average - PTA4 and per frequency), Adaptive speech in noise and Speech in quiet tests will be carried out in order to objectively assess hearing performance with the two sound processors. These tests are all relevant and objective methods used by clinics internationally as a way to assess hearing performance. The same audiological tests were used in the CBAS5539 clinical investigation [1].

The rationale for using Osia SP as comparator against the Osia 2 SP is that both are within the same fitting range, and Osia 2 SP is developed as the next generation sound processor to be used in conjunction with the OSI100 Implant which is already implanted in the selected subjects. The subjects have used the Osia SP for at least a year when they start this clinical investigation. Hence, it is considered a valid justification for the comparison.

This investigation is limited to adult subjects coming only from the clinic in Melbourne and will include a mix of subjects with conductive hearing loss, mixed hearing loss and SSD.

The rationale for the chosen follow-up period is based on the following: In terms of time required for acclimatisation/patients being used to a hearing device, there is no consensus in the literature, especially in terms of speech recognition. However, within audiology and based on clinical experience, it is expected that subjective acclimatisation would occur somewhere between 30-60 days after first fitting. All subjects to be enrolled are used to hearing through bone conduction with their Osia SP. The period of 6 weeks is estimated to be long enough for the subjects to adapt and get used to the hearing performance with the Investigational device, but still not override the experience of the previous sound processor. The subjects’ experience from both devices should be as up-to-date as possible.

In the current investigation, none of the subjects will have an acclimatisation period with the Osia SP as they are already familiar with this device and use it on a daily basis (i.e. acclimatisation has already taken place). However, it is important to highlight that all subjects enrolled in the current study have taken part of the CBAS5539 study, meaning that they all have recently been optimally fitted. In addition, these subjects were informed that they could contact the clinic as needed after completion of that study. Thus, the probability of the subjects coming in at visit 1 with an ill-fitted Osia SP is low.

4.3 Overall objectives and measurements

Overall objective	**Measurements**
To compare the subjects' overall preference regarding the Osia 2 SP and Osia SP	• Preferred choice made by selection between Osia 2 SP and Osia SP • Self-reported assessments ➢ Abbreviated Profile of Hearing Aid Benefit (APHAB) ➢ Speech, Spatial, and Qualities of Hearing Scale (SSQ) ➢ Self-reported assessment regarding satisfaction and usability (QUEST version 2) • Audiometric thresholds in free field ➢ Thresholds audiometry, free-field [PTA4, Mean of 0.5, 1, 2 and 4 kHz]. ➢ Thresholds audiometry, free-field [0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0 and 8.0 kHz]. • Speech recognition tests in quiet and noise ➢ Adaptive speech in noise [speech-to-noise ratio, 50% speech understanding]. Osia 2 SP vs Osia SP at 6 weeks ➢ Speech in quiet [% correctly perceived words at 50dB, 65dB and 80dB SPL]. Osia 2 SP vs Osia SP at 6 weeks.

Overall objective	Measurements
To assess the subjects' experience regarding Comfort and specific usage	• Subjective experience regarding comfort and specific usage ➢ Comfort ➢ Magnet choice ➢ Battery life ➢ SoftWear pad use ➢ Safety line use ➢ Wireless accessories

Safety objective(s)	Outcome measure(s)
Adverse Events and concomitant medication/treatment	Information will be collected from visit 1
Device deficiency	Information will be collected from visit 1

5 PROCEDURES

Procedures that will be performed during the clinical investigation are outlined in the flow chart, see Synopsis and Section 7. In this clinical investigation, Visit 2 can either be performed as a visit at the clinic or as a telephone contact, as required by the subject.

5.1 Test equipment

The test set-up regarding speaker placement, sound room facility and software used at each clinic shall be checked and approved by the Sponsor prior to inclusion of the first subject in the investigation. All tests shall be performed in a sound isolated room. Equipment used for audiological testing shall be calibrated before initiation of the investigation. Calibration certificates will be asked for by the Sponsor as part of the study documentation. It is important to keep the sound room set-up for the speech perception testing and free field testing unchanged during the entire clinical investigation. Changes are not allowed. However, baseline audiograms can be performed in a separate room using audiological standards

If, for some exceptional reason, any significant changes would be needed with the test equipment during the investigation a new calibration needs to be performed. Calibration documentation should be kept with the Investigator File.

5.2 Inform Consent and eligibility criterias

At Visit 1, informed consent must be obtained before any investigational procedures starts During this visit all the inclusion and exclusion criteria should also be checked and fulfilled.

5.3 Demographics

The following demographic data will be recorded at Visit 1:

- Age collected as date of birth (month and year)
- Gender
- Ethnicity

5.4 Medical history

The following information will be recorded at Visit 1:

- Current concomitant medication and treatments and 6 months back.

5.5 Baseline characteristics

During Visit 1, a number of baseline characteristics will be recorded:

- Treatment ear (indicate left or right)
- Type of hearing loss: (Conductive, Mixed or SSD)
- Aetiology: (chronic) infection, tumour, trauma, malfunction, otosclerosis, other reason

5.6 Audiogram

Unaided audiometric threshold measures (including both air- and bone conduction thresholds) should demonstrate that the subject has a conductive hearing loss, mixed hearing loss or SSD and is a suitable subject for the Osia 2 SP as per the third inclusion criteria.

An existing audiogram may be used as long as it has been completed during the last six months and contains all the required relevant frequencies. (250, 500, 750, 1000, 1500, 2000, 3000, 4000, 6000 and 8000Hz), with a PTA4 of ≤55dB for conductive or mixed and PTA4 of ≤20dB in the non-test ear for single-sided sensorineural deafness.

If an audiogram is older than 6 months, does not contain the required frequencies or the subject experience a change in hearing, a new audiogram has to be performed at Visit 1. Frequencies required for air conduction thresholds are 250, 500, 750, 1000, 1500, 2000, 3000, 4000, 6000 and 8000Hz. Frequencies required for bone conduction thresholds are 250, 500, 750, 1000, 1500, 2000, 3000, 4000 and 6000Hz. Contralateral masking should be used if needed, and according to local practice. The hearing care professional shall always record the unmasked threshold and record the masked if applicable.

Note: for SSD subjects it is acceptable to use an audiogram older than 6 months that confirms the type of hearing loss as SSD. However, an audiogram not older than 6 months for the hearing ear is required.

5.7 Sound Processor Fitting

The Osia Fitting Software (currently released version at the time of the start of investigation) will be used to adjust the Osia 2 SP settings for a specific subject.

Prior to the study start it should be ensured that the subjects to be included are completely satisfied with the Osia SP settings as part of the normal clinical routine. The subjects will be asked before the inception of the study whether they are satisfied with their current fitting or if they want to make any adjustments in Osia SP. Hence, during Visit 1, we perceive them to be as optimally fitted as possible with the current device (i.e. Osia SP).

This will enable the subjects to answer the questions at Visit 1 in the most appropriate way.

At Visit 1 the subjects will then receive the Osia 2 SP which should be used during the following 6 weeks. Fitting of the Osia 2 SP will be performed in the same way in order to achieve the best possible hearing situation for the subjects. At Visit 2 or any extra visit adjustments for Osia 2 SP will be possible.

In this investigation the aim at Visit 3 is that the subjects are satisfied with the wearing comfort and sound in the SP, and that no further adjustments are required before initiating the audiology tests and answering any questions.

5.7.1 Magnet selection

At Visit 1 the most suitable magnet should be selected for the sound processor to be tested, and the current instruction for use should be followed. It is important that the strength is not too weak or too strong. There are 4 different strengths, starting from 1 to 4. During Visit 2

and any extra visit the choice of sound processor magnet should be checked for the most optimal comfort. There may be a need to decrease or increase the strength depending on the subject's preference.

5.7.2 Digital Link Calibration

The Digital Link Calibration (e.g. coil-to-coil measurement) which is a step in the connection step in the Osia Fitting Software, should be performed at first fitting and potentially at Visit 2 or any extra visits if it is needed. For the Osia 2 SP this data will be collected, saved on the provided laptop and eventually transferred to the Sponsor for analysis.

5.7.3 Feedback measurement

A feedback measurement is performed to establish the Individual Stable Gain and should be performed at Visit 1 and as required at Visit 2 and any extra visit. For the Osia 2 SP this data will be collected, saved on the provided laptop and eventually transferred to the Sponsor for analysis.

5.7.4 Bone conduction (BC) Direct

BC Direct is a tool in the Fitting Software to establish the unmasked bone condition threshold with tones presented through the sound processor. BC Direct should be performed at Visit 1 and as required at Visit 2 and any extra visits. All generated BC Direct data shall be collected and saved for further analysis. BC thresholds obtained at the following frequencies will be recorded; 250, 500, 750, 1000, 1500, 2000, 3000, 4000, 6000 Hz.

5.7.5 Fine tuning

Fine tuning will be performed as required during Visit 1 when the subject first receives the Osia 2 SP, and potentially at Visit 2 or any extra visits as needed. At Visit 3 the aim is that the subjects is satisfied with the sound in the SP, and no further fine tuning is required. The OFS will be installed on a laptop provided by the Sponsor, and the fitting data will be saved on the laptop and being transferred to the Sponsor in a coded way.

5.8 Randomised device test order

The order in which Osia SP and Osia 2 SP will be tested for each subject at Visit 3, will be randomised to reduce the risk of bias. See example for two subjects in table below.

Subject 1			
Osia SP	Thresholds audiometry	Speech in quiet	Speech in noise
Osia 2 SP	Thresholds audiometry	Speech in quiet	Speech in noise
Subject 2			
Osia 2 SP	Thresholds audiometry	Speech in quiet	Speech in noise
Osia SP	Thresholds audiometry	Speech in quiet	Speech in noise

6 MEASUREMENTS

Measurements employed in the clinical investigation are outlined in the flow chart, see section 7.

During the measurements, the signal processing of the sound processors will be standardised according to given instructions found in a separate Work Instruction which will be available by the time of study start. This will also be included in the site staff training material handed out at the Site Initiation Visit.

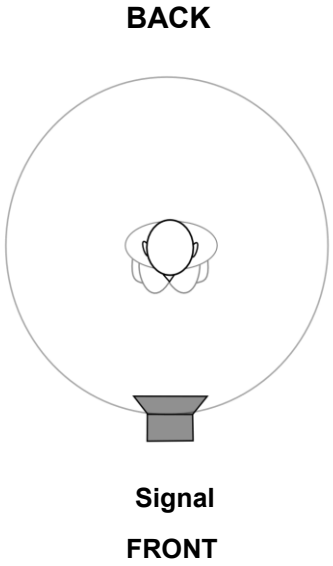
All tests shall be performed with the non-test ear blocked (in case of normal or near-normal hearing or a large asymmetry with the non-test ear having significantly better hearing thresholds). Before blocking of the non-test ear a free-field measurement on PTA4 frequencies (500, 1000, 2000, 4000 Hz)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

6.1 Free-field thresholds audiometry

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 5). The signal to be used should be Warble Tones.

At Visit 3, free-field thresholds shall be measured aided with the Osia 2 SP and the Osia SP according to the randomised device test order under section 5.8. Both sound processors will be tested according to the settings given in a separate final Work Instruction by the time of the study start.

Figure 5. Free field front speaker position.

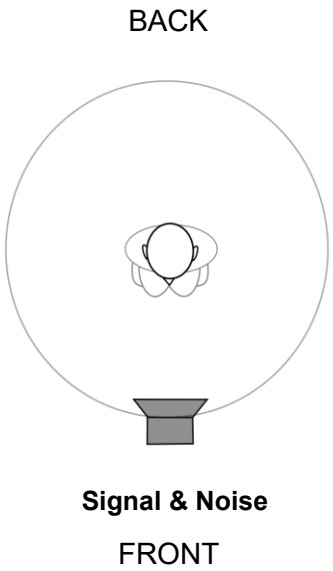


6.2 Speech recognition in noise

The purpose of this test is to establish the test subject's ability to recognise speech in the presence of background noise. Software and speech material to be used is the AuSTIN [6]. The AuSTIN test is an adaptive speech-in-noise test with a 4 talker babble noise and shall be conducted using validated lists. The speech and babble noise signals presented in free field from the front (0 degrees azimuth) (Figure 6). 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.

The speakers should be at the height of the test subject's head and at least 1 metre away from the test subject. There should preferably be more than 1 metre of free space around the test subject in all directions. This is in accordance with the current standard [7].

Figure 6. Speech in noise test speaker position and signal and noise presentation.



At Visit 3, the speech in noise test will be performed aided with the Osia 2 SP and the Osia SP according to the randomised device test order. Both sound processors will be tested according to the settings given in a separate final Work Instruction by the time of the study start.

6.3 Speech recognition in quiet

The purpose of this test is to establish the test subject's word recognition score in quiet. The speech test in quiet shall be performed using phonetically balanced words presented in free field through a speaker from the front (0 degrees azimuth) (Figure 5). The test material shall be monosyllabic words and presented at 50, 65 and 80 dB sound pressure level (SPL) and scores shall be recorded as % correct words at each presentation level. At Visit 3, the

speech in quiet test will be performed aided with the Osia 2 SP and the Osia SP according to the randomised device test order.

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

The APHAB form "A" questionnaire 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 situation [2]. APHAB produces a global score and scores for four subscales: ease of communication, reverberation, background noise, and aversiveness. The APHAB questionnaire is available for free and in a number of different translations on the HARL home page, http://www.harlmemphis.org

The subjects will complete the APHAB questionnaire at Visit 1 and 3 by rating the **aided subscale only** (i.e. no rating of the non-aided subscale will be assessed in this study).

- At Visit 1, the subjects shall complete the questionnaires and the questions shall be answered with respect to "pre-study experience" using the Osia SP.
- At Visit 3, the subjects shall complete the questionnaires answering with respect to the past 6 week period using the Osia 2 SP.

NOTE: at Visit 3 the questionnaire should be answered by considering the Osia 2 SP alone without the Wireless accessories.

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

The short form of Speech, Spatial, and Qualities of Hearing questionnaire (SSQ-12) from MRC Institute of Hearing Research, UK, is a scaled-down version of the 49 items SSQ questionnaire. 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 [3]. The SSQ-12 questionnaire has been approved for use for free by the MRC Institute of Hearing Research. 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 Visit 1 and 3.

- At Visit 1, the subjects shall complete the questionnaire and the questions shall be answered with respect to "pre-study experience" using the Osia SP.

- At Visit 3, the subjects shall complete the questionnaire answering with respect to the past 6 week period using the Osia 2 SP.

NOTE: at Visit 3 the questionnaire should be answered by considering the Osia 2 SP alone without the Wireless accessories.

6.6 The Quebec User Evaluation of Satisfaction with assistive Technology (QUEST version 2)

During the clinical investigation at Visit 1 and 3 information regarding the subject's preference regarding aesthetics, comfort, usage time and ease of use will be collected. At Visit 1 for Osia SP, at Visit 3 for the past 6 weeks period using the Osia 2 SP. Questionnaire to be used for these assessments is the Quebec User Evaluation of Satisfaction with assistive Technology (QUEST) version 2.

The QUEST is an outcome measurement instrument designed to evaluate a person's satisfaction with his or her assistive technology device. It can be used with adolescents, adults and elderly persons who as a result of a physical or sensory impairment have acquired an assistive technology device. The assistive devices targeted include seating and mobility aids environmental control units, hearing and visual aids as well as aids to assist in the performance of daily living activities.

The QUEST form displays the scoring of the 12 satisfaction items in two parts: Device (eight items) and Services (four items). The satisfaction items related to the characteristics of the device are: 1) dimensions, 2) weight, 3) adjustments, 4) safety, 5) durability, 6) simplicity of use, 7) comfort and 8) effectiveness. In the current investigation, the service part of the questionnaire will not be employed as the purpose is not to evaluate the service surrounding the experimental device. Each item is scored using a 5-point scale ranging from 1 to 5, where: 1 (dissatisfied), 2 (somewhat satisfied), 3 (more or less satisfied), 4 (very satisfied), to 5 (totally satisfied). The examiner must record the number of invalid answers. The subscale scores of each domain are calculated by adding the valid answers and dividing the sum by the number of items for each subscale. Moreover, the questionnaire lists 12 satisfaction items and prompts the user to choose the three most important items.

Studies of the QUEST have shown high internal consistency reliability and validity [4].

NOTE: at Visit 3 the questionnaire should be answered by considering the Osia 2 SP alone without the Wireless accessories.

6.7 Comfort and specific usage

Similar to the CBAS5539 clinical investigation, a visual analogue scale (VAS) will be used to capture the comfort experienced by the subject. Subjects will be asked to complete this at Visit 1 for Osia SP and at Visit 3 for Osia 2 SP. Subjects will also be asked questions regarding the choice of magnet for Osia 2 SP, battery change and the use of SoftWear Pad:

- Comfort: By visual analogue scale 100 mm. Subject will be asked to put a line where they find most appropriate:

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

Not comfortable at all — *Most comfortable imaginable*

- Magnet choice: What strength of magnet was chosen for Osia 2 SP at Visit 1. If there is a need for magnet change this will be captured at Visit 2 or any extra visit.
- Change of battery: How often do you change battery, what is the estimated average battery life? For Osia SP at Visit 1 and for Osia 2 SP at Visit 3.
- SoftWear Pad: Do you use SoftWear Pad? No/Yes – Frequency for change? For Osia SP at Visit 1 and for Osia 2 SP at Visit 3.
- Safety Line: Do you use the Safety line? No/Yes. For Osia SP at Visit 1 and for Osia 2 SP at Visit 3.

6.8 Use of Wireless (WL) accessories and iPhone apps

At Visit 1 the subjects should choose at least one of the available accessories stated below. The audiologist will instruct the subject on how to connect and use the chosen accessory(ies) according to each User Manual [8,9,10].

Between Visit 1 and Visit 3 the subjects should be encouraged to use the accessory(ies) as much as possible.

- Cochlear Wireless Phone-clip
- Cochlear Baha Remote control 2
- Cochlear Wireless Mini-microphone 2+

At Visit 3, open follow-up questions should be asked to capture the subjects' experience:

- *Which of the WL accessories did you use?*
- *In what situations did you use the accessory(ies)*
- *For how long time did you use them on average?*
- *Experienced benefit or difficulty with the accessory(ies)*

For subjects using iPhone it will also be possible and encouraged to pair their iPhone to the Osia 2 SP and use the wireless features. This will enable the user to; change volume, program and stream music and sound via the iPhone.

At Visit 3, open follow-up questions should be asked to capture the subjects' experience:

- *Did you pair and use your iPhone together with the Osia 2 SP?*
- *In what situations did you use the Osia 2 SP with the iPhone?*
- *For how long time did you use the Osia 2 SP with the iPhone on average?*
- *Experienced benefit or difficulty with the paired iPhone?*

6.9 Subject's overall preference

For the Overall Objective, the subject shall at Visit 3 decide the preferred choice based on their subjective experience of the overall hearing performance together with the sound quality, aesthetics, comfort, and usability experience of the sound processors.

- The subject should in relation to this final choice indicate what influenced his/her decision the most (several options possible):
    - *Hearing performance*
    - *Sound quality*
    - *Aesthetic*
    - *Comfort and sound processor ease of use*
    - *Possibility to use Wireless accessories*
    - *Possibility of iPhone pairing*
    - *Other (free text)*

6.10 Adverse event and device deficiencies

6.10.1 Device deficiency reporting

The definition of a device deficiency is ”an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.”

Any a device deficiency observed will be fully investigated by the investigator and documented in the electronic case report form (eCRF).

A device deficiency that could have led to a Serious Adverse Event (SAE) should be reported immediately (see next section).

6.10.2 Adverse Event (AE) and Serious Adverse Event (SAE)

6.10.2.1 Definitions

Term	Definition
Adverse Event (AE)	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 used in the investigation. NOTE 1 This definition includes events related to the investigational medical device or the comparator. NOTE 2 This definition includes events related to the procedures involved.
Adverse Event of Special Interest (AESI)	An AESI is an AE of scientific and medical concern specific to the sponsor’s product(s). The reporting requirements from the investigator to CBAS for an AESI will be the same as the reporting requirements for an SAE
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device
Serious Adverse Event (SAE)	Adverse event that a) led to death b) led to serious deterioration in the health of the subject, that either resulted in • a life-threatening illness or injury • a permanent impairment of a body structure or a body function • in-patient or prolonged hospitalization • medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment • to a body structure or a body function c) led to foetal distress, foetal death or a congenital abnormality or birth

	defect **Note** - Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event
Unanticipated Serious Adverse Device Effect USADE	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report

6.10.2.2 Handling and reporting of AEs and ADEs

Subjects will be carefully monitored during the investigation for possible adverse events and appropriate treatment of the subject will be initiated, starting from Visit 1 until Visit 3.

Any adverse events observed will be fully investigated by the investigator and documented in the eCRF including assessment of seriousness, severity (mild, moderate or severe) and relationship to the medical device.

6.10.2.3 Definition of AESI in this clinical investigation

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

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

6.10.2.4 Handling and reporting of AESIs, SAEs and device deficiency that could have lead to a SAE

An investigator should report within 24 hours, after being aware of the event, an AESI, SAE or a device deficiency that could have led to a SAE. The report shall be sent via the eCRF to Cochlear Bone Anchored Solutions AB (Sponsor). If this is not possible the SAE report form should be send via email or fax to the Sponsor. Contact information is available on the paper version of the SAE form.

6.10.3 Reporting to ethical committees and regulatory authorities

SAEs/SADEs/USADEs and device deficiencies that could have led to a SAE should be reported to ethics committees and regulatory agencies in accordance with local requirements.

6.11 Concomitant medication(s) and treatment(s)

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

7 FLOW CHART

Procedures and timing	Visit 1	Visit 2/ Contact*	Visit 3
Day/Week/Month	Day 0	14 days	6 weeks
Time window		± 5 days	± 5 days
Demographics	X		
Medical history	X		
Eligibility criteria	X		
Audiogram	X		
Baseline characteristics	X		
Informed consent	X		
Sound Processor Fitting			
Magnet choice	X[1]	X[3]	
Digital link calibration (DLC)	X[1]	X[3]	
Feedback measurement	X[1]	X[3]	
BC Direct	X[1]	X[3]	
Fine tuning[1]	X[1]	X[3]	
Randomised device test order			X
Thresholds audiometry, free-field			X
Speech recognition in noise			X
Speech recognition in quiet			X
APHAB	X[2]		X[1]
SSQ	X[2]		X[1]
QUEST	X[2]		X[1]
Comfort and Specific usage: Comfort, magnet choice, battery life, SoftWear pad, Safety line	X[2]		X[1]
Wireless accessories			X[1]
Subject´s overall preference			X[4]
Adverse events	X	X	X
Device deficiency	X	X	X
Concomitant treatment	X	X	X
Extra visit			

*Visit 2 is optional as a Visit. Can be done by contact via phone call

[1] Investigational device

[2] With Comparator

[3] As required, Investigational device

[4] Investigational Device vs Comparator

8 RISK AND BENEFITS OF THE INVESTIGATIONAL DEVICE(S) AND THE CLINICAL INVESTIGATION

8.1 Anticipated clinical benefits

All subjects to be enrolled in this clinical investigation have previously been part of the CBAS5539 clinical investigation performed at the same clinic, as part of an international multicentre study. They have all ended and completed that clinical investigation and follow up is supposed to be performed according to normal clinical practice. Each patient was able to keep the sound processor (the comparator Osia SP) used in the previous clinical investigation according to approval by ethics committee.

Taking part in this clinical investigation will not provide or mean any immediate or considerable clinical benefit compared to normal clinical practice except that the patients will get some extra follow up and attention for 6 weeks once the investigation has started.

One outcome that could be seen as a considerable benefit taking part in this clinical investigation is that all subjects will receive an upgrade of the Osia sound processor during the clinical investigation. This upgrade, the Osia 2 SP, is technically more advanced, smaller and lighter. The Osia 2 SP will not yet be available for the market, which is beneficial for the subjects participating in the investigation. The participants will also be offered to keep the Osia 2 SP once the investigation is completed.

8.2 Anticipated adverse device effects

The complaints received from subjects with this type of device may be related to magnetic retention issues of the sound processor. Considering that the Osia 2 SP is smaller and has less weight, the retention issue is judged as limited or absent. Skin irritation has not been reported so far for the precursor device, Osia SP, in the ongoing CBAS5539 clinical investigation. For Osia 2 SP no additional new risks are anticipated compared to the previous Osia SP, see Hazards Analysis Osia 2 Sound Processor [11].

8.3 Residual risks associated with the investigational device

There are not residual risks associated with the Osia 2 SP.

8.4 Risks associated with participation in the clinical investigation

The Sponsor does not consider that there are any specific risks associated with participating in the clinical investigation, compared to the potential risks present in normal clinical practice.

8.5 Control and mitigation of risks

Participating investigators are very experienced and have more than one year of experience from the Osia System, with the previous Osia SP and the OSI100 Implant. They also know their patients very well as they are not new patients. Each patient will be followed up for these 6 weeks and monitored for any adverse events.

At the time of finalising this Clinical Investigation Plan, testing, validation and verification activities are completed, ongoing or to be initiated as specified in the Investigators Brochure

(IB) [12]. Necessary activities to ensure safety and technical performance for study subjects will be completed and reported according to the IB before any study specific activities begin.

8.6 Risk-to-benefit assessment

The risks have been judged acceptable when weighed against the benefits of the intended performance of the investigational device.

8.7 Safety Assessment

The Sponsor will do the Safety Monitoring within the study team at Cochlear Bone Anchored Solutions and use a Medical Advisor as judged necessary. The Medical Advisor is an independent ENT surgeon contracted for use by Cochlear for medical questions and advice.

The Sponsor study team keeping the entire data of the safety situation of the device being tested, also based on the previous CBAS5539 study, will continuously review the reported events in this study. Once there are events reported that are outside what is normally reported and are related, possibly related or unexpected the responsible Study Lead contacts the independent Medical Advisor to ask for a judgment and opinion. This could lead to further contact with the reporting site to clarify or advise. By using and training the site of the term AESI, Adverse Event of Special Interest (section 6.10.2.3) the Sponsor also ensure that the site will report any specifically interesting or unusual events in the same way as Serious Adverse Event (within 24 hours).

9 STATISTICAL CONSIDERATION

9.1 Statistical design and general statistical methodology

No formal statistical testing will be made between Osia 2 SP and Osia SP. The study is not dimensioned to present or test significances by groups/subgroups.

All variables will be presented descriptively by Osia 2 SP and Osia SP where applicable. The change/difference between Osia 2 SP and Osia SP (with 95% confidence interval for the mean difference) will be calculated and presented.

Continuous variables will be presented with mean, standard deviation, standard error of the mean, median, minimum, maximum and number and categorical variables with number and percentage.

All measurements will be made on the Full analysis set except for the safety variables which will be presented for the Safety population.

9.1.1 Sample size calculation

Only subjects who completed the CBAS5539 clinical investigation at the Melbourne site will be included in this clinical investigation. No sample size calculation is made. Up to 12 subjects will be included.

9.1.2 Analysis sets – populations

Full analysis set consist of all subjects attending the 6 weeks visit. Safety population consists of all subjects attending Visit 1.

9.2 Overall objective analyses

The results will be presented by Osia 2 SP and Osia SP and for the change/difference as described 9.1 *Statistical design and general statistical methodology*.

9.3 Safety analyses

Adverse events, concomitant medication/treatment and device deficiency will be presented descriptively for the Osia 2 SP.

9.4 Interim analysis

No interim analyses are planned to be performed.

9.5 Statistical Analysis Plan

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

10 STATEMENT OF COMPLIANCE

10.1 Ethical requirements for the conduct of the investigation

The investigation will be conducted in accordance with the ethical principles as described in the latest version of the Declaration of Helsinki adopted by the World Medical Association.

The Clinical Investigation Plan (CIP), the informed consent form and any other written information that will be given to subjects will be submitted to the appropriate ethics committee.

The investigation shall not begin until approval/favourable opinion from ethics committee has been obtained.

10.2 Regulatory requirements for the conduct of the investigation

This investigation involves a device that is not regulatory approved in the EU, (not received CE mark) nor is it approved by the Australian Authority, TGA. The clinical investigation is a single centre investigation only involving an Australian site, therefore the investigation does not need formal approval from regulatory authority TGA. But the investigation shall not begin until a notification has been acknowledged by the TGA.

The investigation will be conducted in accordance with applicable local regulations, e.g. data protection legislation.

10.3 Updates

The appropriate ethics committee shall after initial approval of the investigation receive the following information:

- Status reports and written summary of the investigation as required by the ethics committee
- Documentation required in order to apply for an extension
- Documentation required in order to apply for an amendment to the CIP or the informed consent form
- Report(s) with new information that may affect the safety of the subjects or the conduct of the study

A protocol amendment must be approved by concerned ethics committee.

10.4 Quality standards

The staff at the investigational site and the Sponsor shall follow the guidelines provided in the ISO standard ‘Clinical investigation of medical devices for human subjects – Good clinical practice (ISO 14155:2011)’.

11 ADMINISTRATIVE ASPECTS

11.1 Training

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

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

11.2 Investigational data

11.2.1 Case report form

Data Collection will be done by using an electronic system (eCRF) for each subject in which information will be reported. Specific instructions on how to complete the eCRF will be provided to the investigator and other site staff. Completed eCRFs will be reviewed and signed by an investigator.

11.2.2 Patient questionnaires

As part of the investigational data the sponsor will gather information using patient questionnaires. These will be administrated separately from the eCRF but entered into the same database.

11.2.3 Source data

Source data is defined as all the information in original records, certified copies of original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation.

The eCRF could be source data and before the initiation of the investigation the principal investigators should together with the CRA complete the template ‘Origin of source data’ stipulating where source data should be recorded at the investigational site.

11.2.4 Data management

A data management plan will be written that describes the overall data handling process including data validation, clarification of data and the clean file process.

All outstanding questions regarding data should be taken during the clean file meeting. After declaring clean file, the data will be locked.

11.3 Archiving

The sponsor and principal investigator shall maintain the investigation documents as required by the applicable regulatory requirements.

11.4 Device accountability

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

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

a) the date of receipt,

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

c) the expiry date, if applicable

d) the date of being used

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 investigational devices

11.5 Quality control

11.5.1 Monitoring

The sponsor will appoint a monitor that will visit sites during the investigation. The monitor will be appropriately trained and informed about the nature of the investigation, ISO 14155:2011 and applicable regulatory requirements.

The monitoring process (including access to source data and extent of source data verification will be described in a monitoring plan.

The monitor will verify the informed consent of participating subject, that the investigational team is adhering to the protocol and that data are accurately recorded in the eCRF.

The monitor must have direct access to source data.

11.5.2 Audit

Audits of the clinical investigation may be conducted by the sponsor or third party designated by the sponsor to evaluate compliance with the CIP, written procedures, ISO-14155:2011 and applicable regulatory requirements.

11.6 Clinical Investigation Plan

11.6.1 CIP amendment

Changes to this CIP must be described in an amendment that is signed by the sponsor and Principal investigator. Necessary approvals must have been obtained before the amendment can be implemented.

11.6.2 Deviations from Clinical Investigation Plan

Investigators are not allowed to deviate from the CIP unless under emergency circumstances, deviations from the CIP to protect the rights, safety and well-being of human

subjects may proceed without prior approval of the sponsor and the EC. Such deviations shall be documented and reported to the sponsor and the EC as soon as possible.

Any deviation from the CIP will be recorded together with an explanation of the deviation. Deviations will be reported to the sponsor, who is responsible for analysing them and assessing their significance. The appropriate ethics committee will be informed of any significant protocol deviations.

11.7 Suspension or premature termination

The sponsor may suspend or prematurely terminate the clinical investigation for significant and documented reasons. The Principal investigator may suspend or prematurely terminate participation in the clinical investigation at the investigation site for which he is responsible.

Circumstances that may warrant termination include, but are not limited to:

- Suspicion of an unacceptable, significant or unacceptable risk to subjects

- Insufficient adherence to protocol requirements repeatedly identified during monitoring or auditing

In case of suspension or premature termination the sponsor shall remain responsible for providing the resources to fulfil the obligations of the protocol and existing agreements for following up the subjects that are enrolled in the clinical investigation.

11.8 Publication policy

The result of this study will be published in accordance with the "WHO *statement on public disclosure of clinical trial results"* in which it is stated that trial results should both be submitted for publication in a peer reviewed medical journal and posted in the result section in the primary clinical trial registry:

- The submission to a peer reviewed journal should occur within 12 months of study completion (last subject, last visit) and the results should be publicly available within 24 months of study completion.
- In addition, the key outcomes are to be made publicly available within 12 months of study completion by posting the results in the primary clinical trial registry.

Authors of the primary publication based on this study must fulfil the criteria defined by the International Committee of Medical Journal Editors (ICMJE).

The primary publication must be published before any secondary publications are submitted for publication.

11.9 Timetable

First subject first visit	Q1 2019
Last subject first visit	Q1 2019
Last subject last visit	Q2 2019

11.10 Definition of end of investigation

End of investigation is defined as “last subject last visit”.

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