Clinical Investigation Plan (CIP)

Investigation code	CBAS5539
Version	5
Version date	14 Aug 2017

Clinical performance of a new implant system for bone conduction hearing

Open, two-armed prospective, multicentre clinical investigation. 3-month investigation (primary analysis) with an additional 9 months of follow-up.

NCT03086135

This CIP version 5 includes the following additions:

CIP version	Date	Comments
1	25 September 2016	Submitted in Australia
2	24 January 2017	Including Amendment 1
3	05 March 2017	Including Amendment 2
4	31 March 2017	Including Amendment 3 Will be submitted in US and EU

5	14 August 2017	Including Amendment 4: Update following Bfarm and FDA review Will be submitted in EU and Australia

SYNOPSIS

Name of Sponsor	Cochlear Bone Anchored Solutions AB
Investigation code	CBAS5539
Investigational title	**Clinical performance of a new implant system for bone conduction hearing**
Design	Open, two-armed, prospective, multicentre clinical investigation. Three-month investigation (primary efficacy analysis) with an additional 9 months of follow-up. Primary safety analysis is based on an endpoint at 6 months.
Investigational device(s)	ATB System (Osseointegrated Steady State Implant System, commercially to be named Osia™ System)
Comparator(s)	No comparator will be used.
Aim for conducting the investigation	The aim of the investigation is to demonstrate that the ATB System provides an improvement in hearing outcomes and quality of life compared to unaided hearing in patients with a conductive or mixed hearing loss or single-sided sensorineural deafness (SSD). The aim is also to measure and present preoperative audiological test results with a Baha BP110 Power Sound Processor on a Baha Softband in relation to the Investigational device.Safety parameters will be collected.
Inclusion criteria	• Adult subjects (18 years or older) • Subject with conductive or mixed hearing loss in the ear to be implanted. Bone conduction thresholds with pure tone average (PTA4; mean of 0.5, 1, 2 and 4 kHz) of ≤ 55 dB. **OR** Subject with single-sided sensorineural deafness who is a candidate for Baha surgery. 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 OR subject who is indicated for an AC CROS but—for some reason—cannot or will not use an AC CROS (Air Conduction-Contralateral Routing of Signal). • Signed informed consent. • Previous experience from amplified sound through properly fitted amplification . (For example but not limited to Hearing aid, CROS device, Bone conductional hearing device on headband/ softband)
Exclusion criteria	• Uncontrolled diabetes as judged by the investigator. • Condition that could jeopardise osseointegration and/or wound healing (e.g. osteoporosis, psoriasis, long-term systemic use of

	corticosteroids) or condition that may have an impact on the outcome of the investigation as judged by the investigator. • Insufficient bone quality and quantity for implantation of a BI300 Implant. • Use of ototoxic drugs that could be harmful to the hearing, as judged by the investigator • Unable to follow investigational procedures, e.g. to complete quality of life scales. • Participation in another clinical investigation with pharmaceutical and/or device. • Subject that has received radiotherapy in the area of implantation, or is planned for such radiotherapy during the study period. • The subject is pregnant or lactating • The subject suffers from psychiatric and/or psychosomatic disorder(s).
Number of subjects	• 50 evaluable subjects (visit 2 performed successfully).
Duration of subjects participation	• One year in total (3 + 9 months)

Objectives and outcome measures	
Primary objective	**Outcome measure(s)**
To compare hearing performance with the Investigational device and the unaided hearing situation	At 3 months • Thresholds audiometry, free-field [PTA4, Mean of 0.5, 1, 2 and 4 kHz]. Investigational device (at 3 months) vs. Unaided. • Adaptive speech in noise [speech-to-noise ratio, 50% speech understanding]. Investigational Device vs. Unaided (preoperative).

Secondary objective(s)	**Outcome measure(s)**
To compare hearing performance with the Investigational device and the unaided hearing situation	• Thresholds audiometry, free-field [PTA4, Mean of 0.5, 1, 2 and 4 kHz]. Investigational Device (4w, 6 and 12 months) vs. Unaided (preoperative). • Thresholds audiometry, free-field [0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0 and 8.0 kHz]. Investigational Device (4w, 3, 6 and 12

	months) vs. Unaided (preoperative). • Adaptive speech in noise [speech-to-noise ratio, 50% speech understanding]. Investigational Device (4w, 6 and 12 months) vs. Unaided (preoperative). • Speech in quiet [% correctly perceived words at 50dB, 65dB and 80dB SPL]. Investigational Device (4w, 3, 6, and 12 months) vs. Unaided (preoperative). • Feedback measurements. Investigational Device (Visit 4 and onwards).
To compare the self-reported assessments of hearing outcome with the Investigational device and in a preoperative hearing situation	• Abbreviated Profile of Hearing Aid Benefit (APHAB). Investigational Device at 3 and 12 months vs. preoperative hearing situation. • Health Utilities Index (HUI23S1EN.15Q) at 3 and 12 months. Investigational device vs. preoperative hearing situation • Speech, Spatial and Qualities of Hearing Scale (SSQ) at 3 and 12 months. Investigational device vs. Unaided.
To collect surgical information	• Soft tissue thickness • Soft tissue reduction performed • Type of anaesthesia • Surgery time • Bone polishing/removal at the actuator site • BI300 Implant length • Location of BI300 Implant • Surgical incision type/location
To collect information about the magnet choice and daily use of sound processor	• Daily usage time • Comfort • Softpad use • Choice of magnet strength
To measure hearing performance preoperatively with a Baha BP110 Power Sound Processor on a Baha Softband	• 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 in quiet [% correctly perceived words at 50dB, 65dB and 80dB SPL] • Adaptive speech in noise [speech-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].

Tertiary objective	**Outcome measure(s)**
To measure hearing performance preoperatively with a current hearing aid (if used by the patient).	• Adaptive speech in noise [speech-to-noise ratio, 50% speech understanding].

Safety objective(s)	**Outcome measure(s)**
Primary safety analysis at 6 months.	
Implant site evaluations	Numbness
Adverse Events and concomitant medication/treatment	Information will be collected from visit 2 and onwards.
Device deficiency	Information will be collected from Visit 2 and onwards.
Audiogram	Bone conduction thresholds preoperative and postoperative (3, 6, and 12 months).

Flowchart

	Visit 1 Pre-op testing	**Visit 2** Surgery	**Visit 3** Suture removal	**Visit 4** Fitting	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**
Visit time point		**0**	**2W**	**4W**	**6W**	**3M**	**6M**	**12M**
Visit window			± 5D	± 1W	± 1W	± 2W	± 3W	± 4W
Demographics	X							
Medical history	X							
Baseline characteristics	X							
Audiogram	X					X[6]	X[6]	X[6]
Eligibility criteria	X							
Informed consent	X							
Soft tissue thickness	X or X							
Surgery[1]		X						
IOTS		X						
Suture removal			X					
Sound processor fitting	X[2]			X	X	X	X	X
Magnet choice				X	X	X	X	X
BC Direct	X[2]			X	X	X	X	X
Feedback measurements				X	X	X	X	X
Free field thresholds	X[2,3,4]			X		X	X	X
Speech recognition in quiet	X[2,3, 4]			X		X	X	X
Speech recognition in noise	X[2,3, 4]			X		X	X	X
APHAB	X[3]					X		X
HUI	X[4]					X		X
SSQ	X[3]					X		X
Daily use[5]					X	X	X	X
Numbness			X	X	X	X	X	X
Device deficiency		X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X
Concomitant medication/treatment		X	X	X	X	X	X	X
Extra visits as needed								

[1] *Surgical variables: Soft tissue thickness (mm), Surgery time (time between first incision and last suture), Bone polishing/removal at the actuator site, BI300 Implant length (4mm, 3 mm), Location of BI300 Implant (mm), Type of anaesthesia (general, local), Soft tissue reduction performed (yes, no), Surgical incision type.*

[2] *BahaPower Sound Processor (BP110) on Baha Softband*

[3] *Unaided*

[4] *In a preoperative hearing situation*

[5] *Daily use: Usage time (hours/day), Comfort (visual analogue scale), Softpad use*

[6] *Only bone conduction*

TABLE OF CONTENTS

ABBREVIATIONS

APHAB	Abbreviated Profile of Hearing Aid Benefit
AC-CROS	Air Conduction-Contralateral Routing of Signal
ADE	Adverse Device Effect
AE	Adverse Event
AESI	Adverse Event of Special Interest
AIMD	Active Implantable Medical Device
ATB-System	Active Transcutaneous Bone conduction System
CBAS	Cochlear Bone Anchored Solutions AB
CE	Conformité Européenne
CI	Cochlear Implants
CIP	Clinical Investigation Plan
CRO	Contract Research Organisation
EC	Ethic Committee
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
FS	Fitting Software
HARL	Hearing Aid Research Lab
HRQL	Health Related Quality of Life
HUI23S1EN.15Q	Health Utility Index 23 Self-Administered English 15 Questions
IFU	Instruction For Use
IOTS	Intraoperative Test System
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intention To Treat
OFS	Osia Fitting Software
PTA4	Pure Tone Average 4
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
WHO	World Health Organisation
PP	Per Protocol
USADE	Unanticipated Serious Adverse Device Effect

1 INTRODUCTION

1.1 Background

1.1.1 The Baha Systems

The Cochlear™ Baha® bone conduction systems offers two alternative ways to transmit vibrations from the external sound processor to the osseointegrated implant: The Baha Connect System uses a skin-penetrating abutment and allows *direct* bone conduction. The passive Baha Attract System uses a magnetic connection through intact skin. Magnetic conduction have the advantage over skin-penetrating systems of eliminating the daily cleaning, reduction in reported adverse skin reactions of the implant site and are perceived as more cosmetically appealing by many subjects. The skin-penetrating abutment of the traditional Baha System is seen as a barrier for many candidates. The passive Baha Attract System was developed in consideration of all these features and incorporates implantable and external parts as illustrated in Figure 1.

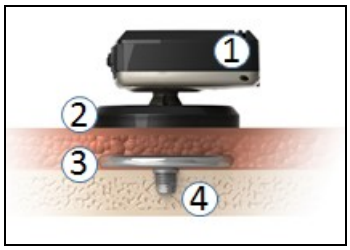

Figure 1: The passive Baha Attract System

The sound processor (1) is connected (via a snap coupling) to the sound processor magnet (2), which, together with the implant magnet (3), constitute the transcutaneous coupling. The implant magnet is fixated to the titanium implant (4).

Both Baha Systems make use of the same external sound processors and are built on the same implantable platform, the osseointegrated BI300 Implant. Both systems have been proven to be safe and effective through years of clinical use and data from clinical investigations[1, 2, 3]. While the Baha Connect System enables direct bone conduction through the percutaneous implant, the passive transcutaneous Baha Attract System offers less efficient bone conduction (especially at high frequencies) due to attenuation of sound vibrations through the intact skin that separates the external transducer from the osseointegrated implant.

1.1.2 The ATB System

The ATB System (Osseointegrated Steady State Implant System) is developed to provide the benefits of a non-skin-penetrating system combined with the benefits of a skin-penetrating system. Compared to the passive transcutaneous Baha Attract System, the ATB System will provide a more efficient transmission of sound, especially in the high frequency range, as the implantable transducer eliminates the attenuation of sound vibrations through the soft tissue that is inherent to the passive system. With the ATB System it will also be possible to position the transducer closer to the ear canal, which may further improve audiological outcomes.

The ATB System is a bone-conduction hearing device that allows direct bone-conduction through an implanted actuator on the osseointegrated BI300 Implant (Figure 2).

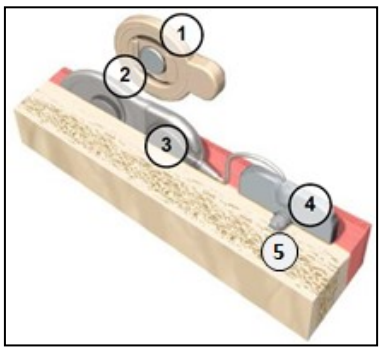

Figure 2: The ATB System

The ATB System function as follows:

- The external sound processor - SP (1) captures and digitally processes sound
- The SP transmits power and digital information to the internal implant (2)
- The implant converts the digital information into a an electric analogue implant (3)
- This electric signal is transmitted to the actuator (4)
- The actuator converts the electric signal to vibrations that are transmitted to the mastoid bone trough the osseointegrated BI300 Implant (5)

With the ATB System the following transition paths have been established:

- From a traditional percutaneous solution – the Baha Connect System
- Via a magnetic connection solution (Baha Attract System) with better aesthetics but limited performance due to skin attenuation, especially in the high frequency area
- To the ATB System which combines aesthetics with higher performance to meet the needs of subjects with mixed hearing loss. The target fitting range is 55dB Sensorineural hearing loss (SNHL). In addition, since the actuator creating the vibration is connected directly to the BI300 Implant, the attenuation of higher frequencies that occurs when using the Baha Attract System, could be avoided.

1.2 Aim

The aim of the investigation is to demonstrate that the ATB System provides an improvement in hearing outcomes and quality of life compared to unaided hearing in patients with a conductive or mixed hearing loss or single-sided sensorineural deafness (SSD).

The aim is also to measure and present preoperative audiological test results with a Baha BP110 Power Sound Processor on a Baha Softband in relation to the Investigational device. Safety parameters will be collected.

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

2.1 Investigational device

2.1.1 Description of the investigational device(s)

The ATB System is intended for patients with conductive or mixed hearing loss, or single-sided sensorineural deafness (SSD). Patients should have sufficient bone quality and quantity to support successful implant placement. This system should only be used by trained, qualified professionals. The ATB System has a fitting range of up to 55 dB SNHL bone conduction threshold in mixed hearing loss.

The regulatory classification of the system is expected to be Class III active implantable medical device (AIMD) in the EU and Class II or III in the US[1]. The instruments of the ATB System that have previously been CE marked and FDA cleared for the current Baha or Cochlear Implant (CI) systems maintain their current classification. The BI300 Implant will also maintain its classification in the EU (Class IIb) and in the US (Class II).

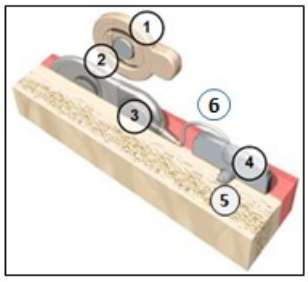


Figure 3: The ATB System parts:1 Sound Processor, 2 Receiver, 3 Stimulator, 4 Actuator, 5 BI300 Implant, 6 Lead

The ATB System (Figure 3) consists of the following components:

Button sound processor (1):

The ATB Sound Processor (SP) 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 ATB SP has identical hardware as the CP950 Sound Processor for Cochlear Implants, but with ATB specific firmware. The ATB SP will commercially be referred to **Osia™ Sound Processor.**

The sound is picked up by the microphone and processed by the processing unit. It is sent to the active coil which transmits the signal to the implant coil. The processing unit also contains light emitting diodes (LED) and one command button, which allows the patient to control the processing unit e.g. switching the sound processor on/off. Power to the sound processor is provided by two 675 Zinc-Air batteries which are accessed by removal of the battery cover. A SoftWear™ Pad (also used with the Baha Attract Sound Processor Magnet) will be available, which distributes the force imposed by the magnets and reduces point pressures on the skin (Figure 4). Complete information for the ATB SP is found in the user manual [4].

[1] *To be confirmed.*

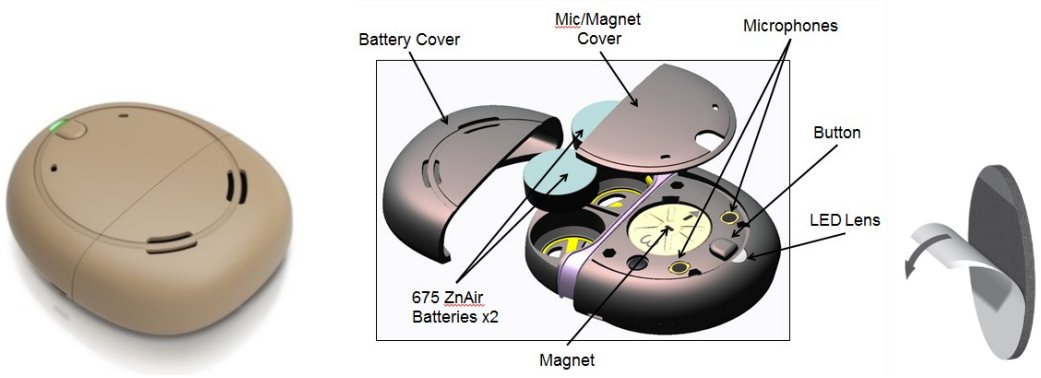


Figure 4. Left: Osia Sound Processor, external view (upper surface). Middle: Osia Sound Processor, partially exploded view. Right: SoftWear™ Pad, showing removal of protective film to expose self-adhesive surface.

ATB-Implant (OSI100 Implant) consist of:

Receiver- stimulator (2 and 3)

The coil, magnet and case in the receiver-stimulator is reused from the Freedom Cochlear Implant platform (CI24RE), which has been used in Cochlear implantable systems since 2005. The Codacs® system also use identical coil, magnet and case. A magnet located at the centre of the implant coil allows the coil of the external sound processor to be placed in the correct position, over the receiver-stimulator coil. The receiver-stimulator contains ATB specific electronics, which is powered by two batteries in the external sound processor. The receiver-stimulator is completely over-moulded by a silicone coating.

Actuator (4)

Actuator is a piezoelectric transducer which converts the signal into corresponding vibrations. The actuator design concept is conceived of a piezo-bender connected to two identical tungsten moving masses. When the piezo-element is electrically driven by the stimulator electronics, a vibration is generated at the central fixation clamp, the location where the actuator is fixed to the BI300 Implant. All external weld seams of the ATB Actuator are over-moulded by a silicone coating. See figure 5.

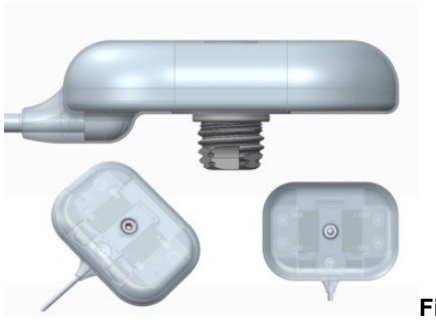


Figure 5. : The ATB Actuator

The design of the Actuator reuses critical design features from the BIM400 Implant magnet of the Baha Attract System. The size of the actuator, including the silicone coating, measures 31.4 × 22.6 x 4.9 mm. The Actuator will come pre-mounted on the Isolator inside the sterile blister packaging, being prepared for the IOTS testing, see section 2.3.4.

Lead (6)

Actuator is connected to the receiver-stimulator via a standard Cochlear lead (currently used in the CE marked Codacs® System). The lead is over-moulded by a silicone coating.

CP950 Magnets

The CP950 magnets come in 6 various strengths; ½ (weakest) to 6 (strongest). The CP950 magnets are identical as the magnet used in the CP950 Sound Processor for Cochlear implants and are therefore regulatory approved and bear CE marking. They are used according to their intended use.

BI300 Implant (5)

The ATB System uses the same osseointegrated BI300 Implant for anchorage in the bone as in existing Baha Connect and Baha Attract systems and is identical to the Cochlear Vistafix VXI300 Implant which all are regulatory approved. The BI300 Implant bears CE marking and comes in two different lengths, 4mm and 3 mm and is made of titanium. The surface is moderately roughened (TiOblast™) on its intraosseous parts. The BI300 Implant is used according to their intended use.

Table 1 lists the investigational device used in this clinical investigation.

Table 1. List of Investigational device.

Name	Description	Part Number
Osia Sound Processor	Sandy Blonde Chocolate Brown Slate Grey Black	P798664 – P798667
OSI100 Implant	- Receiver-Stimulator (coil, magnet, case) - Actuator (including isolator) - Lead	Z398787
CP950 Magnets	Strength from 0.5 – 6	Z566412, Z502922, Z502923, Z502924, Z502925, Z566414, Z566415
BI300 Implant	4mm, 3 mm	92129, 92128

Complete information for the ATB implant is found in the professional user guides [5, 6].

2.1.1.1 Manufacturer of investigational device(s)

Cochlear Limited, Sydney, Australia	Osia Sound Processor ATB Implant CP950 Magnets
Cochlear Bone Anchored Solutions AB	BI300 Implant

2.1.2 Description of comparator

No comparator will be used in this clinical investigation. All patients will be their own control.

2.2 Blinding

No blinding will be used in this clinical investigation.

2.3 Other devices used in the investigation, non-investigational

2.3.1 Surgical instruments

The surgical procedure for the ATB System combines steps of the recommended surgical procedure for implantation of the BI300 Implant, the BIM400 Implant Magnet of the Baha Attract System, and the receiver-stimulator assembly of CI24RE. Hence, ATB surgery reuses existing surgical tools and templates for Baha and CI surgery. There are only 4 new surgical tools and 1 new template (sterile and non-sterile versions) specific to the ATB System. Table 2 lists the recommended surgical instruments for ATB surgery. The ATB specific surgical instruments used to prepare the bone bed for the ATB Actuator reuse design features of the instruments that are used to prepare the bone bed for Baha Attract surgery; different instrument design is required due to the different shape of the ATB Actuator compared to Baha Attract implant magnet (rectangular versus circular).

Table 2. ATB surgical instruments

Instrument	Description	Part Number
New surgical instruments		
ATB specific Reusable Instruments	Actuator Template	P772551
	Clearance indicator	P772552
	OSI100 Recess checking gauge	P795943
ATB specific Single Use Instruments	OSI100 Single use kit (Sterile, single use) Includes: Guide Pin, OSI100 template	Z496667
	OSI100 template (Non sterile, single use)	P794316
Existing surgical instruments		
Cochlear Baha Reusable Instruments	Screwdriver Unigrip 95mm	90469
	Multi wrench with ISO adapter	92143
	Machine Screwdriver Unigrip 25mm	90381
	Implant inserter	92142
	Drill indicator	91116
	Soft tissue gauge 6 mm	95070
	Raspatorium	90944
	Dissector	90943
	Baha ruler	93339
Cochlear Baha Single Use Instruments	Conical guide drill 3+4 mm	93363
	Widening drill 3mm	92140
	Widening drill 4mm	92141
Cochlear Nucleus Reusable Instruments	Bone Recess Template	Z60479
	Array Exit Marking Template	Z33017

More information about the new ATB specific instruments and template are found in **Appendix 1.** Complete information for the ATB surgical instruments is found in the professional guides [5, 6].

2.3.2 Fitting Software (FS)

Two different fitting software platforms will be used for fitting of sound processors during this clinical investigation, the Baha Fitting Software (BFS) (currently released version) for the reference device Baha Power Sound Processor, and the Osia™ Fitting Software (OFS) CSDS Clin Trial version 1.02 for evaluation of the ATB Sound Processor.

The investigator shall use the BFS to configure the Baha BP110 Power Sound Processor for each subject/user at visit 1. Communication between the fitting software and the sound processor shall be achieved using a Hi-Pro 2 programming interface from GN Otometrics (GNO) and a Programming Cable Long Blue/Red (Figure 6).

The investigator shall use the OFS to configure the operational features of the Osia Sound Processor for each subject/user at visit 4. Communication between the fitting software and the sound processor is achieved using a Freedom Programming Pod, Cochlear Nucleus Programming Shoe with Cable as well as CP950 Programming Shoe Adaptor Cable Kit and two Battery ZN Air P675 Implant Plus.

This fitting software for the Osia Sound Processor version 1.02 is built on and has equivalent graphical user interface and features as the current regulatory approved Baha Fitting Software (BFS). Complete information is found in the Instruction For Use (IFU) [7, 8].

Figure 6. Programming set-up for a BP110, Hi-Pro2 and computer

2.3.3 Programming pod

The Freedom Programming Pod, approved and used for Cochlear's CI products, will be used as it is with the ATB System. The programming pod provides a connection between the programming computer and the ATB Sound Processor via a USB cable and a programming shoe with cable as well as an adaptor cable kit and two batteries.

2.3.4 Intraoperative test system

An intraoperative test system Osia ™ Intraoperative Test System (IOTS) CSDS Clin Trial version 1.01 will be available to confirm device integrity at the time of implantation. An intraoperative test system is available and in use for Cochlear Implants and Codacs to verify the functionality. For ATB System, the IOTS will evaluate any potential damages to the piezo-element and to the lead before surgical closure. The integrity test will be a mandatory step of the surgical procedure, and will be performed just before the actuator is mounted onto the BI300 Implant. The IOTS functions by measuring the

current consumed by the implant's audio circuitry (including the actuator). The measured frequency response provides an indication of the state of the actuator and of the actuator lead.

The test system concept is similar to the existing intraoperative tests available for CI and Codacs, and uses a number of similar and/or identical components (including a computer with dedicated software, Osia Sound Processor, Freedom Programming Pod, Cochlear Nucleus Programming Shoe with Cable as well as CP950 Programming Shoe Adaptor Cable Kit and two Battery ZN Air P675 Implant Plus (Figure 7). The test also relies on the use of a custom silicone Isolator to provide mechanical isolation for the actuator during the test (Figure 8). The Isolator will come pre-mounted on the actuator inside the sterile blister packaging. During the test the receiver-stimulator will already be in place under the patient's skin and the actuator will be mounted in the Isolator (which is secured to the BI300 Implant using the Guide pin). The test takes approximately two minutes to perform, and the software provides the user with an unambiguous test result regarding device integrity prior to closing and suturing the surgical site. A Signal Check wand (currently available for CI and Codacs) is also available to check the radio-frequency (RF) link between the transmitting coil of the sound processor and the internal coil in case of no response from the implant is received during the intraoperative test. The sound processor should be switched on and the Signal Check wand held to the coil. If the signal check lights up the coil is working.

1. Adapter cable
2. Battery retention clip
3. Clothing clip

Figure 7. Intraoperative Test System (IOTS) concept

Figure 8. ATB Implant, with actuator pre-mounted onto the Isolator.

2.3.5 Reference device

The ATB System will provide similar output and audiological performance as the Cochlear Baha BP110 Power Sound Processor. The BP110 Power Sound Process will be used as reference device in this clinical investigation. The BP110 Sound Processor on a Softband will be used at the first visit for the subject, before the surgery visit, to measure preoperative Sound Processor performance and to prepare the subject for the postoperative hearing situation. The BP110 Sound Processor is a fully programmable, head-worn sound processor, with automatic signal processing, which is regulatory approved for use together with Baha systems (Baha Connect and Baha Attract) and together with a Baha Softband (Figure 9). This sound processor is secured to the Baha Softband by means of a snap coupling. The sound processor has several automatic systems, including active feedback cancellation through phase cancellation, automatic adaptive multi-band directional microphones, wide dynamic range compression and automatic noise management. The transducer is driven by a size 675 battery.

Figure 9. Cochlear Baha BP110 Power Sound Processor and Baha Softband

All other non-investigational devices, are listed in Appendix 2.

2.3.5.1 Manufacturer of the non-investigational devices

Cochlear Limited, Sydney, Australia	• ATB specific Reusable Instruments • ATB specific Single Use Instruments • Cochlear Nucleus Reusable Instruments • Osia™ Fitting Software CSDS Clin Trial version 1.02 • Freedom Programming Pod • Osia™ Intraoperative Test Software CSDS

	Clin Trial version 1.01 • Cochlear Nucleus Programming Shoe with Cable CP950 Programming Shoe Adaptor Cable Kit Battery ZN Air P675 Implant Plus • Signal Check (Wand)
Cochlear Bone Anchored Solutions AB	• Cochlear Baha Reusable Instruments • Cochlear Baha Single Use Instruments • Baha BP110 Power Sound Processor • Baha Fitting Software (currently released version) • Baha Softband (Unilateral)

2.4 Treatment after the completion of the investigation

After the clinical investigation the subjects will be able to continue with their investigational device (ATB System). Routine controls with audiological checks will follow local routines according to the standard treatment program for similar devices (e.g. active, non-skin penetrating, bone-conduction hearing devices).

The ATB Implant is expected to have a lifetime of at least 10 years. Any changes to the ATB Implant during or after this time-period should be performed according to the ATB Implant revision/replacement procedure described in the professional guide [5].

After this clinical investigation, it will be possible to use future upgrades of the ATB Sound Processor, used together with the ATB Implant.

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:

- Adult subjects (18 years or older)
- Subject with conductive or mixed hearing loss in the ear to be implanted. Bone conduction thresholds with pure tone average (PTA4; mean of 0.5, 1, 2 and 4 kHz) of ≤ 55 dB HL.

  OR

  Subject with single-sided sensorineural deafness who is a candidate for Baha surgery. 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 OR subject who is indicated for an AC CROS but—for some reason—cannot or will not use an AC CROS (Air Conduction-Contralateral Routing of Signal).
- Signed informed consent
- Previous experience from amplified sound through properly fitted amplification. (For example but not limited to Hearing aid, CROS device, Bone conductional hearing device on headband/ softband).

3.1.2 Exclusion criteria

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

- Uncontrolled diabetes as judged by the investigator.
- Condition that could jeopardise osseointegration and/or wound healing (e.g. osteoporosis, psoriasis, long-term systemic use of corticosteroids) or condition that may have an impact on the outcome of the investigation as judged by the investigator.
- Insufficient bone quality and quantity for implantation of a BI300 Implant.
- Subject that has received radiotherapy in the area of implantation, or is planned for such radiotherapy 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, e.g. to complete quality of life scales.
- Participation in another clinical investigation with pharmaceutical and/or device.
- The subject is pregnant or lactating
- The subject suffers from psychiatric and/or psychosomatic disorder(s).

3.2 Number of subjects

Fifty (50) evaluable subjects (visit 2 performed successfully) will be recruited at five international clinics in order to meet the requirement for recruitment in the investigation. The number of subjects to be included for each centre will be approximately 10. The sponsor will be able to control the inclusion by distribution of devices to each centre.

3.3 Duration of subject participation

Subjects will participate during a 12-month period in total.

3.4 Subject enrolment and Informed consent

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

- The rationale, aims and objectives of the investigation
- Risks and benefits
- Alternative treatments
- Extent of the subject's involvement
- That the subject can withdraw his/her consent at any time
- That the confidentiality of patient data will be maintained at all time
- That the subject will be informed if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial

The subject must have the opportunity to ask any questions. Signed and dated informed consent from potential subjects must be obtained before any investigational procedure can be performed. The investigator will, after informed consent has been obtained, assign a consecutive enrolment number to the subject according to given instructions, e.g. centre 1, subject 101, 102, 103 etc. Centre 2, subject 201, 202, 203 etc.

3.5 Randomisation

This is an open study with no comparator device. Randomisation is not possible.

3.6 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, e.g. implant loss

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.

3.7 Replacement of subjects

If a subject discontinues his/her participation in the investigation, he/she will not be replaced if this discontinuation occurs after surgery is performed. If this discontinuation occurs before surgery the subject will be replaced in order to reach 50 evaluable subjects.

3.8 Insurance

In case of any damage or injury occurring during the participation in the investigation, the Sponsor has contracted an insurance company, Willis 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, two armed, prospective, multicentre clinical investigation and is divided into a 3-month period (primary efficacy analysis) followed by an additional 9 months of follow-up for the complete 12 months period. The primary safety endpoint is 6 months. One arm is selected for conductive and mixed hearing loss subjects, the other arm is selected for single-sided sensorineural deafness subjects. Each subject will be compared to his/her own preoperative unaided hearing situation, with the Baha BP110 Power Sound Processor on a softband preoperatively and with the Investigational device at 3 months. If applicable subjects with a current hearing amplification will also be tested preoperatively.

4.2 Justification for the design of the clinical investigation

The design where the primary assessment consist of a comparison of the post-operative aided performance with the preoperative unaided performance is considered relevant for this purpose. The primary efficacy assessment of the investigation, i.e. threshold, free-field, pure tone average PTA4, is a relevant and objective method used by clinics internationally as a way to assess hearing performance. The test is not language specific (no words used), thus rendering comparative data in an international, multilingual setting.

The self-reported assessment of hearing outcome using the APHAB questionnaire was chosen as an important secondary efficacy assessment; hence, the APHAB scale was used for determination of the sample size in the investigation[9]. The APHAB has been used in investigations previously and has shown to be a good tool for measuring changes in patient benefits.

The rationale for measuring and collect data with Baha BP110 Power Sound Processor on a Softband as a secondary assessment is based on the fact that the FDA guideline for middle ear implants suggests that a comparative non-inferiority or superiority study design (using within-patient comparison) may be required.

The Baha BP110 Power Sound processor on a Softband was chosen for a secondary assessment, since the ATB System mimics the performance of a Baha Power Sound Processor (with the same 55 dB fitting range) on the passive transcutaneous Baha Attract System[1]. Therefore it is also a relevant choice to present as a postoperative hearing situation for the subject.

This investigation is limited to adult subjects. The paediatric population constitutes an inhomogeneous patient group (age-related), and currently there are no audiological tests that are suitable for comparisons across age ranges and across multiple countries/languages.

The follow-up period of 12 weeks post-surgery, 8 weeks post fitting for the primary analysis is chosen as it is judged as long enough for the subjects to adapt and get used to the hearing performance with this investigational device. The total length of the investigation is judged long enough to collect hearing performance and safety data as long term data.

4.3 Objectives and outcome measures

Primary objective	**Outcome measure(s)**
To compare hearing performance with the Investigational device and the unaided hearing situation	At 3 months • Thresholds audiometry, free-field [PTA4, Mean of 0.5, 1, 2 and 4 kHz]. Investigational

	device (at 3 months) vs. Unaided. • Adaptive speech in noise [speech-to-noise ratio, 50% speech understanding]. Investigational Device vs. Unaided (preoperative).

Secondary objective(s)	**Outcome measure(s)**
To compare hearing performance with the Investigational device and the unaided hearing situation	• Thresholds audiometry, free-field [PTA4, Mean of 0.5, 1, 2 and 4 kHz]. Investigational Device (4w, 6 and 12 months) vs. Unaided (preoperative). • Thresholds audiometry, free-field [0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0 and 8.0 kHz]. Investigational Device (4w, 3, 6 and 12 months) vs. Unaided (preoperative). • Adaptive speech in noise [speech-to-noise ratio, 50% speech understanding]. Investigational Device (4w, 6 and 12 months) vs. Unaided (preoperative). • Speech in quiet [% correctly perceived words at 50dB, 65dB and 80dB SPL]. Investigational Device (4w, 3, 6, and 12 months) vs. Unaided (preoperative). • Feedback measurements. Investigational Device (Visit 4 and onwards).
To compare the self-reported assessments of hearing outcome with the Investigational device and in a preoperative hearing situation	• Abbreviated Profile of Hearing Aid Benefit (APHAB). Investigational Device at 3 and 12 months vs. preoperative hearing situation • Health Utilities Index (HUI23S1EN.15Q) at 3 and 12 months. Investigational device vs. preoperative hearing situation. • Speech, Spatial and Qualities of Hearing Scale (SSQ) at 3 and 12 months. Investigational device vs. Unaided.
To collect surgical information	• Soft tissue thickness • Soft tissue reduction performed • Type of anaesthesia • Surgery time • Bone polishing/removal at the actuator site

	• BI300 Implant length • Location of BI300 Implant • Surgical incision type/location
To collect information about the magnet choice and daily use of sound processor	• Daily usage time • Comfort • Softpad use • Choice of magnet strength
To measure hearing performance preoperatively with a Baha BP110 Power sound processor on a Baha Softband	• 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 in quiet [% correctly perceived words at 50dB, 65dB and 80dB SPL]. • Adaptive speech in noise [speech-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].
Tertiary Objective	**Outcome measure(s)**
To measure hearing performance preoperatively with a current hearing aid (if used by the patient).	• Adaptive speech in noise [speech-to-noise ratio, 50% speech understanding].

Safety objective(s)	**Outcome measure(s)**
Primary safety analysis at 6 months.	
Implant site evaluations	Numbness
Adverse Events and concomitant medication/treatment	Information will be collected from Visit 2 and onwards.
Device deficiency	Information will be collected from Visit 2 and onwards.
Audiogram	Bone conduction thresholds preoperative and postoperative (3, 6, and 12 months)

4.3.1 Demographics and baseline variables

Demographics and baseline variables to be collected during visit 1 are the following:

- Demographics

- Medical history
- Baseline characteristics
- Audiogram
- Eligibility criteria (inclusion/exclusion criteria)
- Informed consent

5 PROCEDURES

Procedures that will be performed during the clinical investigation is outlined in the flow chart, see section 6.

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 at the latest during the Site initiation visit. All tests shall be performed in the 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 same sound room and test equipment set-up during the entire clinical investigation. Changes are not allowed.

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 together with a new unaided baseline measurement. Calibration documentation should be kept with the Investigator File.

5.2 Demographics

The following demographic data will be recorded at Visit 1:

- Age collected as date of birth (month and year)
- Gender
- Ethnicity
- Nicotine use (Subjects does not smoke, ≤ 10 cigarettes/day, 11-20 cigarettes/day, 21 40 cigarettes/day, > 40 cigarettes/day)

5.3 Medical history

The following information will be recorded at Visit 1:

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

5.4 Baseline characteristics

During visit 1 a number of baseline characteristics will be recorded;

- Treatment ear (indicate left or right or both. In case of both, indicate side for hearing tests)
- Type of hearing loss: (Conductive, Mixed or SSD)
- Aetiology: (chronic) infection, tumour, trauma, malfunction, otosclerosis, other

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

5.5 Audiogram

Unaided audiometric threshold measures (including both air- and bone conduction thresholds) should demonstrate that the subject has a conductive, mixed hearing loss or single-sided sensorineural deafness and meets the audiological inclusion criteria.

An existing audiogram may be used as long as it has been completed during the last six months, and contains all the required relevant frequencies (250, 500, 750, 1000, 1500, 2000, 3000, 4000, 6000 and 8000Hz). The subject's pre-operative Pure Tone Average PTA4 (mean of 500, 1000, 2000 and 4000Hz) should be computed and recorded to ensure the subject meets the inclusion criteria.

If an audiogram is older than 6 months or does not contain the required frequencies, a new will be performed at Visit 1. Frequencies required for air conduction thresholds are 250, 500, 750, 1000, 1500, 2000, 3000, 4000, 6000 and 8000Hz. 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.

Audiograms for bone conduction thresholds will also be performed at Visits 6, 7, and visit 8 to monitor hearing thresholds postoperatively.

5.6 Soft tissue thickness

At visit 1 or visit 2 (start of surgery), depending on local practice and requirements, soft tissue thickness should be measured. For the ATB System, the skin thickness should not exceed 6 mm to ensure optimal retention and system performance. The measurement should be performed in the centre of the marked coil position. For complete instruction see the surgery guide [5].

5.7 Surgery

The surgery, performed at visit 2, does not take account for any particular circumstances or factors relevant to an individual patient or case. Other surgical approaches and variations are practiced and may be more appropriate in certain patient cases. After considering all relevant circumstances, factors and information in each case, the appropriate surgical procedure is determined by the responsible investigator exercising independent medical judgment. Complete information is found in the surgery guide[5].

During surgery the following variables should be collected:

- Surgery time (time between first incision to last suture)
- Bone polishing/removal at the actuator site (yes/no)
- BI300 Implant length (3mm/4mm)

- Location of BI300 Implant (mm from the ear channel), measured horizontally and vertically). Distance from BI300 to receiver/coil (centre to centre). An alternative option to preoperative measurements with a ruler, is to take a lateral skull radiography postoperatively and measure the distance between the implant receiver magnet and the BI300.
- Type of anaesthesia (general/local)
- Soft tissue reduction (yes/no)
- Surgical incision type (C-shaped flap is anterior based for an anterior actuator position or posterior based flap is considered for a more posterior actuator position or other incision type)

At visit 3, approximately 2 weeks after surgery sutures should be removed.

5.8 Intraoperative Test system (IOTS)

At visit 2, in the end of the surgery procedure, the IOTS test should be performed. The test takes approximately two minutes to perform, and the software provides the user with an unambiguous test result regarding device integrity prior to closing and suturing the surgical site. It is crucial that the staff during surgery follow the instruction for use[10]. The software used for the IOTS is installed on a lap-top provided by the Sponsor. The software collects data from transducer of the implant and will make the Sponsor gain understanding of the behaviour and performance of the transducer once implanted on a recipient. IOTS data will be saved on the lap-top until study is ended when it will be transferred to the Sponsor in a coded way.

5.9 Sound Processor fitting

The Baha Fitting Software 4.0 SR2[8] will be used at visit 1 when the fitting procedure should be performed for the Baha BP110 Power Sound Processor as a reference device.

The Osia Fitting Software 1.02[7] will be used to adjust the investigational device sound processor settings for a specific subject. This will happen during Visit 4 when tests will be performed, and throughout the study. The fitting software will be installed on a lap-top provided by the Sponsor, and the fitting-data will be saved on the lap-top until study is ended when it will be transferred to the Sponsor in a coded way.

The Digital Link Calibration (e.g. coil-to-coil measurement) that is a step in the connection step in the Osia Fitting Software, should be performed at each occasion that the software is being used to fit or fine tune the device to optimize the performance of the device throughout the study. This will also provide an indication of the soft tissue thickness.

For the sound processors Individual Stable Gain (e.g. feedback measurements as part of the Fitting Software) the Feedback Analyser should be performed at each occasion that the software is being used to fit or fine tune the device to optimize the performance of the device throughout the study. For the Investigational device this data will be collected, saved and eventually transferred to the Sponsor for analysis.

5.10 Magnet choice

At visit 4 (sound processor fitting) the most suitable magnet should be selected for the sound processor to be tested, and the instruction for use[5] should be followed. It is important that the strength is not too weak or too strong. There are 7 different strengths, starting from ½ to 6. During the following

visits the choice of sound processor magnet should be checked. There may be a need to decrease or increase the strength depending on the subject's preference.

5.11 Bone Conduction (BC) Direct

BC Direct is a tool in the Baha Fitting Software (current version) to establish the unmasked bone condition threshold with tones presented through the sound processor. At Visit 1, BC Direct data shall be collected with the Baha BP110 Power Sound Processor on a Softband and shall be used to calculate the fitting (settings) of the sound processor for the Softband test. BC Direct measurements (as part of the Osia Fitting Software) will also be performed at visit 4 to visit 8 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.

5.12 Simultaneous bilateral

In the case of a subject receiving simultaneous bilateral ATB systems one of the treatment ears will be selected as the investigational ear for efficacy purposes. Speech in noise performance will be documented for the second ear alone and bilaterally. However, efficacy outcomes for the investigational ear only will be pooled with the outcomes measures made for the unilaterally implanted subjects. Investigational ear choice will be as judged by the responsible investigator prior to surgery. Patient-reported outcomes (APHAB, SSQ and HUI), will be collected post-surgery in a bilateral situation. Safety-related information, including adverse events, will be collected and reported for each ear receiving the ATB system.

6 ASSESSMENTS

Assessments that will be performed during the clinical investigation is outlined in the flow chart, see section 8.

During the assessments, the signal processing of the sound processors will be harmonised according to given instructions given in the eCRF. This will also be included in the staff training at each participating centre during the site initiations.

6.1 Postoperative audiometric assessment

Bone conduction thresholds for the study ear will be monitored postoperatively, to characterize observed unaided thresholds postoperatively. These measures will occur at visit 6 (3 months postoperative) and 7 (6 months postoperative), once healing and swelling is most likely to be resolved and repeated at visit 8 (12 months postoperative). 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.

6.2 Free-field threshold

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 10). The test 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). The signal to be used should be narrow band noise.

At Visit 1, free-field thresholds shall be measured for the unaided situation and with the BP110 Power Sound Processor on a Baha Softband.

At Visit 4, 6, 7 and 8 this measurement should be performed with the investigational device.

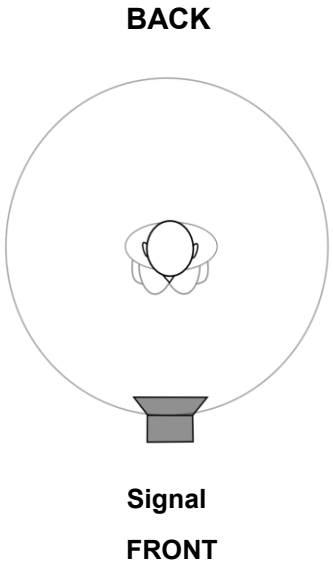


Figure 10. Free field front speaker position.

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 10). 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. The test 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).

At Visit 1, the speech in quiet test shall be performed for the unaided situation and BP110 Power Sound Processor on a Baha Softband.

At Visit 4, 6, 7 and 8 this measurement should be performed with the investigational device.

6.4 Adaptive 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. The adaptive speech test in noise shall be conducted using validated lists of phonetically balanced sentences, with speech presented in free field from the front (0 degrees azimuth) and noise from the back (180 degrees azimuth) (figure 11). 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 speech-to-noise ratio (SNR) providing a 50% level of understanding. Software and speech material to be used is the Matrix test in language specific versions as applicable.
The test 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).

The speakers should be at the height of the test subjects head and more than 1 metre away from the test subject. There should preferably be more than 1 metre of free space around the test subject in all directions. This is in accordance with the current standard[11].

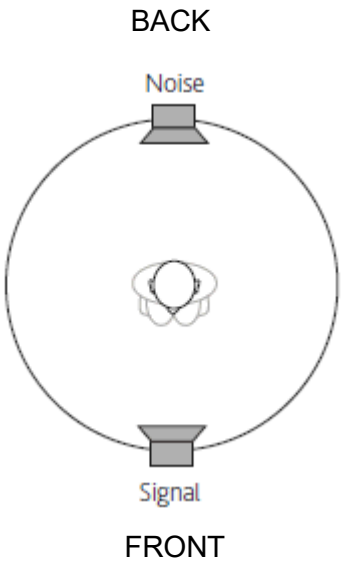


Figure 11. Speech in noise test speaker position

At Visit 1, the speech in noise test will be performed for the unaided situation and BP110 Power sound processor on a Baha Softband. If the subject presents with hearing aids preoperatively, the measurement will also be completed in the subject's test ear in the aided condition.

At Visit 4, 6, 7 and 8 this measurement should be performed with the investigational device.

IMPORTANT: When all audiological tests have been performed and the audiological team is pleased with the data collection, remember to reset the sound processor features according to the patient´s fitting.

6.5 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. APHAB produces a global score and scores for four subscales: ease of communication, reverberation, background noise, and averseness.

The subjects will complete the APHAB questionnaire at Visit 1, 6 and 8.

- At Visit 1, the subjects shall complete the questionnaire prior to the Softband test, and the questionnaire shall be answered with respect to an unaided hearing situation, even for subjects with a previous hearing device.
- At Visit 6 and 8, the subjects shall complete the questionnaire for the aided situation (with the Investigational device).

The APHAB questionnaire is available for free and in a number of different translations on the HARL home page.

6.6 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[12]. 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, 6 and 8.

- At Visit 1, the subjects shall complete the SSQ questionnaire prior to the Softband test and the SSQ questionnaire shall be answered with respect to an unaided hearing situation, even for subjects with a previous hearing device.
- At Visit 6 and 8, the subjects shall complete the questionnaire for the aided situation (with the Investigational device).

The SSQ-12 questionnaires was approved for use in this clinical investigation for free by the MRC Institute of Hearing Research.

6.7 Health Utility Index (HUI23)

The Health Utilities Index (HUI®) 23S15Q is a generic preference-based system for measuring comprehensive health status and health-related quality of life (HRQL). HUI provides descriptive evidence on multiple dimensions of health status, a score for each dimension of health, and a HRQL score for overall health. Health dimensions include vision, hearing, speech, ambulation/mobility, pain, dexterity, self-care, emotion and cognition. Each dimension has 3-6 levels. The version in this clinical investigation uses a recall time of 1 week.

The subjects will complete the HUI at Visit 1, 6 and 8.

- At Visit 1, the subjects shall complete the HUI questionnaire prior to the Softband test and with respect to their current hearing situation
- At Visit 6 and 8, the subjects shall complete the questionnaire for the aided situation (with the Investigational device).

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

6.8 Daily use

During the clinical investigation at visit 5, 6, 7 and 8 data regarding daily use of the sound processor will be collected.

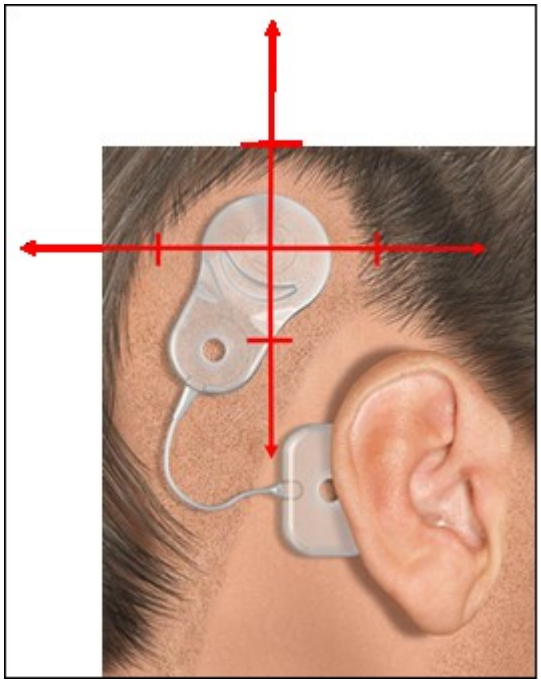
- Average hours of daily use (hours/day) during the last week before Visit 5, and during the last month before Visit 6-8.
- Softpad use (Yes/No) and if yes, frequency of change; number of times the subject changed the Soft pad during the last week before Visit 5, and during the last month before Visit 6-8?
- Comfort (by visual analogue scale 100 mm). Subject will be asked at Visit 5-8:

  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*

6.9 Numbness

Sensibility of the skin directly over the implant is an important outcome measurement to establish a possible difference between surgery with or without skin thinning. Two different sensibilities will be tested by means of a broken wooden cotton swab/bud (q-tip): gnostic (with cotton side) and vital (with broken, sharp wooden side) sensibility. The measurement locations and procedures need to be standardized (Figure12). ATB Implant site evaluations regarding numbness will be performed at Visits 3-8.



- 30 and 60 mm along the lines from the centre of the coil/magnet
- Cranial and caudal and 90 degrees anterior and posterior
- No sampling on the incision line
- The sequence of gnostic/vital stimuli randomly gently applied
- Gnostic sensibility :0-100% 8 locations

  Vital sensibility: 0-100% 8 locations

  Total sensibility: 0-100% 16 trials

Figure 12. ATB Implant site evaluation.

7 ADVERSE EVENT AND DEVICE DEFICIENCIES

7.1 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 case report form (CRF).

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

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

7.2.1 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

7.2.2 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.

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

7.2.3 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 (see section 7.4.2.4):

- 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

7.2.4 Clinically significant threshold shifts

Shifts in threshold, relative to the preoperative baseline, will be reported as an adverse event (AE) when a shift at any frequency exceeds 15 dB HL.

7.2.5 Handling and reporting of AESIs, SAEs and device deficiency that could have led 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 as an email attachment to the safety inbox or faxed to Cochlear Bone Anchored Solutions AB. Contact information is available on the SAE form.

7.3 Reporting to ethical committees and regulatory authorities

SAEs/SADEs/USADEs and device deficiencies that could have led to a SAE shall be reported to ethics committees/institutional review board and competent authorities in accordance with local requirements.

Safety Reporting in Germany

In Germany, a serious adverse event is every unwanted event manifesting in a clinical trial or performance evaluation subject to authorization, which led, could have led or could lead directly or indirectly to the death or a severe worsening of the state of health of a study subject, a caregiver or another person, without considering whether the medical device was the cause of the event (§ 2 No. 5 MPSV). According to the definition of SAEs (in § 2 No. 5 MPSV), every SAE in a clinical trial or performance evaluation subject to authorization must be reported. Therefore, in accordance with § 3 (6) of the Ordinance on Medical Devices Vigilance, for SAEs that occur in Germany that may be device and/or procedure related, Cochlear Bone Anchored Solutions AB or its representatives will use the Report form for reporting of serious adverse events (SAEs) in clinical trials or performance evaluations (SAE Report Form).

All SAE's are reported on forms for reporting of serious adverse events (SAEs) in clinical trials or performance evaluations for use by sponsors according to § 3 (6) of the Ordinance on Medical Devices Vigilance. Timelines for reporting SAE's to the BfArM as described under § 5 MPSV will be adhered to. The reports and messages pursuant to § 3 paragraph 2 to 5 and 6, sentence 3 of the MPSV will be made immediately. All other Serious Adverse events will be fully documented and reported by Cochlear in a summary form on a quarterly basis.

Further according to MPSV §3(6) Cochlear will report Serious Adverse Events to BfArM, which have occurred outside of Germany. If a clinical trial carried out in other parties to the Agreement within the European Economic Area, Cochlear or its representative will report to those competent authorities about Serious Adverse Events that occurred in Germany.

BfArM SAE reporting timelines as described under § 5 MPSV will be adhered to:

Condition for reporting to BfArM	**Country of occurence**	**Timeline for reporting to BfArM**	**Form**
a causal relationship between the SAE and the investigational medical device, a comparator device, diagnostic or therapeutic procedures performed as part of the clinical trial or other conditions of the trial **conduct cannot be excluded**	Germany	immediately	German SAE Report Form for single reports
	all other countries where the clinical trial is performed	immediately	MEDDEV 2.7.3 Summary Table
a causal relationship between the SAE and the investigational medical device, a comparator device, diagnostic or therapeutic procedures performed as part of the clinical trial or other conditions of the trial	Germany	quarterly	MEDDEV 2.7.3 Summary Table (sheet 2)
	all other countries where the clinical trial is performed	quarterly	MEDDEV 2.7.3 Summary Table (sheet 1)

conduct can be excluded			

Safety Reporting in The Netherlands

In the Netherlands serious adverse events will be reported by the sponsor (or its representative Factory CRO for Medical Devices) to the accredited Ethics Committee that approved the protocol and Competent Authorities.

Reporting Timelines to the Ethics Committee:

The Ethics committee requires that all SAEs occurring in all participating sites in the Netherlands and all foreign countries will be reported. The timelines and reporting requirements are as follows:

1. An SAE which indicates an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it: immediately, but not later than 7 calendar days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event.
2. All other SAEs will be reported within 15 calendar days.

Reporting to the Ethics Committee will occur by completing the SAE form in the ToetsingOnline portal (https://toetstingonline.ccmo.nl). These SAEs are automatically forwarded to the Ethics Committee.

Reporting Timelines to the Competent Authority in the Netherlands:

IGZ requires that all SAEs (device-related and not device-related) occurring in all participating sites in all participating countries will be reported.

The reporting timelines are as follows:

1. An SAE which indicates an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it: Immediately, but not later than 2 calendar days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event.
2. All other SAEs will be reported quarterly using SAE line listing according the reporting table of MEDDEV 2.7/3 SAE reporting guidelines.

All SAEs can be reported via email: meldpunt@igz.nl

7.4 Foreseeable Adverse Events

Just like any surgical treatment, OSI100 Implant surgery is not free of risks. Prospective Osia System recipients should be advised of the following possible effects of receiving an implant:

- Normal risks associated with surgery and general anaesthesia

- Increased surgical and anaesthetic risks for certain populations

- Osseointegration failure - Potential causes for failure of osseointegration include lack of adequate bone quantity/quality, trauma, infection, generalised diseases and surgical complications

- Complications that may require additional medical treatment, surgery and/or removal of the device, such as:

i. Acute Otitis Media (AOM)

ii. Concurrent Cerebrospinal Fluid (CSF) leakage

iii. subdural injury

iv. subcutaneous haematoma

v. irritation, inflammation or breakdown of the skin flap; infection; and in some cases, extrusion of the device caused by the presence of a foreign body under the skin.

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

- Failure of various component parts of the implanted device could require removal or replacement of the implant.

7.5 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 case report form. Medication given as standard of care in connection with surgery should not be recorded in the CRF.

8 FLOW CHART

	Visit 1 Pre-op testing	**Visit 2** Surgery	**Visit 3** Suture removal	**Visit 4** Fitting	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**
Visit time point		**0**	**2W**	**4W**	**6W**	**3M**	**6M**	**12M**
Visit window			± 5D	± 1W	± 1W	± 2W	± 3W	± 4W
Demographics	X							
Medical history	X							
Baseline characteristics	X							
Audiogram	X					X[6]	X[6]	X[6]
Eligibility criteria	X							
Informed consent	X							
Soft tissue thickness	X or X							
Surgery[1]		X						
IOTS		X						
Suture removal			X					
Sound processor fitting	X[2]			X	X	X	X	X
Magnet choice				X	X	X	X	X
BC Direct	X[2]			X	X	X	X	X
Feedback measurements				X	X	X	X	X
Free field thresholds	X[2,3,4]			X		X	X	X
Speech recognition in quiet	X[2,3,4]			X		X	X	X
Speech recognition in noise	X[2,3,4]			X		X	X	X
APHAB	X[3]					X		X
HUI	X[4]					X		X
SSQ	X[3]					X		X
Daily use[5]					X	X	X	X
Numbness			X	X	X	X	X	X
Device deficiency		X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X
Concomitant medication/treatment		X	X	X	X	X	X	X
Extra visits as needed								

[1] *Surgical variables: Soft tissue thickness (mm), Surgery time (time between first incision and last suture), Bone polishing/removal at the actuator site, BI300 Implant length (4mm, 3 mm), Location of BI300 Implant (mm), Type of anaesthesia (general, local), Soft tissue reduction performed (yes, no), Surgical incision type.*

[2] *BahaPower Sound Processor (BP110) on Baha Softband*

[3] *Unaided*

[4] *In a preoperative hearing situation*

[5] *Daily use: Usage time (hours/day), Comfort (visual analogue scale), Softpad use*

[6] *Only bone conduction*

CBAS5539 CIP Version 5

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

9.1 Anticipated clinical benefits

The ATB System is an extension of the existing approved Baha product family and is expected to provide the same benefits as these systems in terms of hearing restoration. In addition, the ATB System will provide additional advantages as it combines benefits from both a percutaneous (skin-penetrating) and transcutaneous Baha system

The ATB System provides efficient sound transmission through direct bone conduction, similar to a percutaneous implant**.** Direct bone conduction through a transducer that is directly coupled to the bone is currently only achieved with the percutaneous Baha Connect System. With the active transcutaneous ATB System, the actuator is directly attached to the bone via the osseointegrated BI300 Implant underneath the skin, thus eliminating any loss of energy in the sound vibrations through the skin. Hence, efficiency of sound transmission is on a par with a percutaneous system.

The ATB System provides the cosmetic benefits of a transcutaneous system, such as the Baha Attract System. A percutaneous implant is seen as a barrier and is often rejected by candidates due to cosmetic concerns. A transcutaneous system, without an abutment protruding through the skin, is often perceived as a more aesthetic option.

The ATB System, like the Baha Attract System, will significantly reduce the risk of implant site infections, and eliminates the need for daily maintenance care**.** For the transcutaneous Baha Attract System and ATB System, the implant site is sealed and does not provide a direct path for infections. Skin irritation and/or infection requiring treatment and/or precluding the use of the sound processor are relatively frequent for percutaneous devices due to the exposed abutment and daily site care is required to maintain a reaction-free skin penetration. Some patients are not able—for medical or other reasons—to perform the daily implant site care that the skin-penetration requires.

The ATB System is expected to be associated with a significantly lower risk of osseointegration failure than for the percutaneous Baha Connect System. This risk is expected to be similar to that of the Baha Attract System, which also uses the osseointegrated BI300 Implant. According to the latest post market surveillance reports[13,14] no osseointegration failures have been reported to Cochlear's complaints handling system, nor in the review of scientific literature for the Baha Attract System15.

Transition pathway between the systems. Surgical transition between the three systems (reusing the same osseointegrating BI300 Implant) possible if the patient's needs change over time (provided the location of the BI300 Implant is suitable for the transition).

9.2 Anticipated adverse device effects

Just like any surgical treatment, ATB surgery is not free of risks. Risks associated with the implantation and use of the ATB System cannot be completely eliminated. General risks associated with surgery under general or local anaesthesia apply, and as with any surgical procedure, there is always a risk that unanticipated complications may occur. These risks are expected to be similar for ATB System as for traditional Baha surgery with the Baha Connect and Baha Attract Systems and the procedure for implanting the Cochlear Implants systems (Freedom Cochlear Implant platform (CI24RE) and Codacs® System, see section 2).

Post market surveillance information is collected and those findings relevant for the ATB System is presented below:

9.2.1 ATB Sound Processor (Osia Sound Processor)

The ATB SP has identical hardware as the CP950 Sound Processor for Cochlear Implants, but with ATB specific firmware. Since the CP950 Sound Processor is recently new and no post market surveillance data is yet available, the safety data is based on literature reviews and reviewing the complaints and adverse event (reportable complaint) trending rates for the predicate devices and for the Baha Attract System. The most common complaint is magnetic retention issues of the sound processor. Skin irritation for predicate device is not reported as an issue. For the Baha Attract system skin irritation is fairly common but not reported as a serious problem and often solved by adjusting the magnet strength.

9.2.2 Receiver-stimulator (CI24RE)

During the period 1 July 2009 to Dec 2015, the cumulative number of registered implant surgeries (IS) with CI24RE implants was 153 040 (14 402 surgeries during the last year). Of total number of registered implant surgeries, 80 reportable complaints (0,052% of total IS) have been attributed to the receiver-stimulator. Overall, reportable complaints in the category 'Reliability/quality/defect' occurred at an average rate of 0.006% of the total number CI24RE implant surgeries per month. The complaints are being monitored and there is no upward trend. The majority of complaints in the category 'Medical/surgical issue' have been coded as "Other medical", "Skin flap infection" and "Medical/surgical issue (recipient related)" and the maximum harm for a complaint that was attributed to the device was revision surgery to explant the device.

Based on the post market surveillance activities performed, the CI24RE Series of Implants are considered to be performing in the field within acceptable limits and expectations. All known product issues are appropriately contained, or being managed through existing CAPAs. The Clinical Evaluation Report (411167, Clinical Evaluation Report Nucleus CI24RE Cochlear Implants) provides clinical evidence to establish the acceptability of the risk benefit analysis of the CI24RE Series of Implants[16].

9.2.3 Codacs

During the period 18 October 2013 to 31 October 2015, the cumulative number of registered implant surgeries with Codacs DI110 implant and DF110 Fixation System was 65 (39 during the last year). No reportable complaints were attributed to the receiver-stimulator or the lead. The number of reportable events related to medical/surgical issues or no-fault-found was 2 (3.1%). Based on the post market surveillance activities performed, the Codacs DI110 implant and the Codacs DF110 Fixation System are considered to be performing in the field within expectations (D701349, Post Market Surveillance Report, Codacs DI110 implant and DF110 Fixation system)[17].

9.2.4 BI300 Implant with the Baha Connect System

Since launch in 2010 to Oct 2015, 55 341 BI300 implants (including abutment) have been sold with a reported monthly complaint rate around 0.1-0.2%. The complaint relevant to the ATB System is BI300 implant loss. The rate of implant loss for the Baha Connect System is around 1%. The overall complaint rates and reportable events are well below the pre-defined escalation threshold[14].

9.2.5 BI300 Implant with the Baha Attract System

During the period Aug 2013 to Jan 2017, approximately 11.000 BIM400 (Baha Attract Implant magnet including BI300) have been sold globally. The most commonly reported symptoms are skin reactions and/or pain around the implant magnet and magnet retention issues with an overall rate of up to 2%. The symptoms are usually reported to be mild and treated by adjusting Sound Processor (SP) Magnet strength.

No cases of implant loss due to osseointegration failure have been confirmed. The overall complaint rates and reportable events are well below the pre-defined escalation threshold (D784107, Post Market Surveillance Report, Baha Attract, November 2015)[13].

9.3 Risks associated with participation in the clinical investigation

The Investigational device is reused by several parts from already CE marked products. There is no guarantee that the ATB Implant will not cause any adverse device events. The ATB Implant is expected to have a lifetime of about ten years. By the time of first implantation in the clinical investigation, spring 2017, it will be possible to claim approximately 30 months of equivalent lifetime. Test results will be reported periodically until an equivalent lifetime of 10 years is reached. As with any new surgical product and medical device, there is a risk that unanticipated Adverse Events may occur. The subjects will be closely monitored in the investigation and instructed to contact the responsible investigator if they experience any untoward effect. In the worst case scenario the patient would need a revision surgery to remove the ATB Implant, but this can be done with local anaesthesia. They will then end participation in the clinical investigation and follow normal clinical care and follow up.

9.4 Control and mitigation of risks

The surgical procedure is described in the surgery guide for the ATB System [5]. The guide has been developed by the Sponsor together with a group of experienced Baha and Cochlear Implant surgeons. Although most of the surgical tools are the same as for Baha and CI implantation, there are some new tools provided. These have been validated with presence of experienced implant surgeons during the surgical validation activity (cadaver surgical training and practical evaluation and testing of the surgical tools) and no patient implantation before these performed validation procedures were completed and reported.

Before start of each site in the clinical investigation each investigator will have done documented surgery training according to the surgery guide either at a cadaver lab test or on a plastic skull.

MRI examinations can be performed safely on a person with this implanted device only under very specific conditions. An MRI information package is supplied with each implant for additional information regarding magnetic resonance imaging[18].
Subjects enrolled in the investigation that receive the ATB System will receive an MRI card, for information to radiologists if an evaluation and planning of any MRI examination becomes necessary. Subjects that have received radiation therapy, or are planned for radiation therapy during the investigation, at the same side of the skull where the ATB System will be positioned are excluded from the investigation.

9.5 Risk-to-benefit assessment

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

10 STATISTICAL CONSIDERATION

10.1 Statistical Design and Objectives

10.1.1 Primary statistical objectives

To compare hearing performance with the Investigational device and the unaided hearing situation.

10.1.2 Secondary statistical objectives

- To compare the self-reported assessments of hearing outcome with the Investigational device and in an unaided hearing situation
- To compare hearing performance with the Investigational device and the unaided hearing situation
- To compare the self-reported assessments of hearing outcome with the Investigational device and in a preoperative hearing situation
- To collect surgical information
- To collect information about the magnet choice and daily use of sound processor
- To measure hearing performance preoperatively with a Baha BP110 Power Sound Processor on a Baha Softband
- To measure feedback on the Investigational device

10.1.3 Tertiary statistical objective

To measure hearing performance preoperatively with a current hearing aid (if applicable and not mandatory)

10.2 Efficacy variables/endpoints

10.2.1 Primary variables/endpoints

The primary efficacy analysis will be determined by analysis of change in free-field threshold audiometry: PTA4 (mean of 500, 1000, 2000 and 4000Hz) and change in Adaptive speech recognition in noise (50% performance), from unaided versus Investigational device at the 3 months visit.

- Thresholds audiometry, free-field [PTA4, Mean of 0.5, 1, 2 and 4 kHz]

It is hypothesized that the group mean free-field PTA4 (average of 500, 1000, 2000, and 4000 Hz) with the Osia System at the 3-month postoperative interval will be improved over that measured preoperatively in the unaided condition (baseline).

This endpoint is represented by the following hypotheses:

$$H_0: \mu_F - \alpha_0 \geq 0,$$

$$H_a: \mu_F - \alpha_0 < 0,$$

where:

α_0 = baseline preoperative PTA4;

μ_F = mean follow-up PTA4 3 months postoperative.

- Adaptive speech in noise [speech-to-noise ratio, 50% speech understanding]

It is hypothezied that the group mean Adaptive speech recognition in noise (50% performance), speech to noise ratio (SNR) with the Osia System at the 3-month postoperative interval will be improved over that measured preoperatively in the unaided condition.

This endpoint is represented by the following hypotheses:

$$H_0: \mu_F - \alpha_0 \geq 0,$$

$$H_a: \mu_F - \alpha_0 < 0,$$

where:

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

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

10.2.2 Secondary variables/endpoints

- Abbreviated Profile of Hearing Aid Benefit (APHAB)
- Thresholds audiometry, free-field [0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0 and 8.0 kHz]
- Speech in quiet [% correctly perceived words at 50dB, 65dB and 80dB SPL]
- Feedback measurement
- Health Utilities Index (HUI23S1EN.15Q)
- Speech, Spatial and Qualities of Hearing Scale (SSQ)
- Soft tissue thickness
- Soft tissue reduction performed
- Type of anaesthesia
- Surgery time
- Bone polishing/removal at the actuator site
- BI300 Implant length
- Location of BI300 Implant
- Surgical incision type/location
- Daily usage time
- Comfort
- Softpad use
- Choice of magnet strength
- BC Direct [0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0 and 6.0 kHz]

10.2.3 Safety variables/endpoints

- Numbness
- Adverse Events and concomitant medication/treatment
- Device deficiency
- Audiogram

10.3 Sample size calculation

10.3.1 Sample size calculation for the primary efficacy analysis

In order to achieve 90% power to detect a clinically significant difference of 10 dB in free-field hearing thresholds or 10 dB SNR between the unaided situation and the ATB System at the 3 months visit with Fisher's non-parametric permutation test for paired observations, one-sided test with significance level 0.025, on the ITT population 11 (PTA-4) and 13 (SNR) evaluable subjects are needed. The sample size was calculated using simulation on study id CBAS5675 (Cochlear 2017) data which used the simulated ATB system on Mixed/Conductive subjects. The within subject SD for change Unaided to ATB in PTA4 was 9.5 dB and 11.3 SNR. Since significant result want to be detected in both arms (SSD and Conductive/Mixed) 13+13=26 subjects should be included in the investigation.

10.3.2 Sample size calculation for the secondary analysis

In order to achieve 90% power to detect a clinically significant difference of 15 units in APHAB Benefit between the unaided situation and use of the Investigational device at the 3 months visit with Fisher's one-sided non-parametric permutation test for paired observations, one-sided test with significance level 0.025, on the pooled ITT population (SSD and Conductive/Mixed together), 28 evaluable subjects are needed assuming a within subject standard deviation (SD) of 23.3 units. The within subject SD has been estimated to 23.3 in a previous Cochlear-sponsored multi-centre clinical investigation which compared APHAB scores for pre-operative unaided hearing and for post-operative use of a Baha sound processor mounted on a percutaneous implant over 12 months (Study ID CBAS5439). To compensate for drop out of two patients in the study, 30 subjects should be included in the investigation.

10.3.3 Sample size estimation for the primary safety analysis at 6 months

Primary safety analysis will be evaluated at 6 months and an estimation of 50 subjects results in 25 patient years at 6 months, which will yield enough safety data for the primary safety analysis. At the 12-month analysis 50 subjects results in 50 patient years.

10.3.4 Overall sample size considerations

In order to achieve 90% power both for the primary analysis (PTA4 and SNR, Investigational Device vs. Unaided) and the primary safety analysis, 50 evaluable subjects are needed. Each arm SSD and Conductive/Mixed should at least consist of 13 patients to assure a power of 90% in both arms for the primary analysis.

10.4 General statistical methodology

All statistical analyses will be paired non-parametric. In order to choose the most powerful test, the Fisher's non-parametric permutation test for paired observations will be used for all paired analyses of continuous variables. For paired analysis of dichotomous and ordered categorical variables the Sign test will be used.

The main efficacy analysis will be performed on the ITT population and complementary efficacy analyses will be performed on the PP population. The main analysis will be performed after the 3 month visit. A complementary analysis will be performed 9 months after the main analysis (12-month visit). All significance tests will be one-sided and performed at the 5% significance level.

Imputation of missing values (definitions made in SAP) will be performed for all efficacy variables. No imputation of baseline values or baseline carry forward will be made.

All analyses, tables and figures will be produced for SSD and Conductive/Mixed separately and also pooled as on population.

10.5 Efficacy analysis

10.5.1 Primary efficacy analysis

Primary efficacy analysis will be determined by analysis of change in free-field threshold audiometry: PTA4 (mean of 500, 1000, 2000 and 4000Hz) and change adaptive speech recognition in noise (50% performance), from preoperative Unaided versus Investigational device at the 3 months visit for the ITT population, using Fisher's one-sided non-parametric permutation test for paired observations at a significance level of 0.025 to demonstrate an improvement in PTA4. Each arm SSD and Conductive/Mixed will be tested separately. Both PTA4 and SIQ must be significant at alpha 0.025 for the primary analysis to be considered as confirmative in each arm separately. In addition, a pooled analysis for all subjects will be made.

10.5.2 Secondary efficacy analyses

The second efficacy analyses will be performed for Investigational Device vs. Unaided. Baha BP110 Power Sound Processor on a Baha Softband will be presented (where applicable) but not compared to Investigational Device.

- APHAB
- Threshold audiometry: PTA4 (Mean of 500, 1000, 2000 and 4000 Hz)
- Threshold audiometry: 250, 500, 1000, 2000, 3000, 4000 and 6000 Hz
- Adaptive speech recognition in noise (50% performance)
- Speech in quiet (50dB, 65dB and 80dB)
- HUI-III (compared with current hearing situation)
- SSQ
- Choice of SP magnet
- BC Direct
- Feedback measurements. Investigational device

The secondary analyses will be presented for ITT and PP populations.

10.5.3 Tertiary efficacy analyses

The tertiary analyses will be presented for Current Hearing Aid.

- Adaptive speech recognition in noise (50% performance)

The tertiary analyses will be presented for ITT population.

10.6 Safety analyses

10.6.1 Implant site evaluation

Evaluation regarding numbness will be presented.

10.6.2 Adverse Events

Adverse Events and Serious Adverse Events will be presented overall and by relationship (Device related) both totally and per predefined Adverse Event, System Organ Class and Preferred Term.

10.6.3 Device deficiency

Device deficiency will be presented by visit.

10.7 Analyses of concomitant medications and treatments

Prior and concomitant medication will be summarised.

10.8 Demographics and baseline characteristics

Demographics and baseline characteristics will be descriptively summarised.

10.9 Interim analysis

An interim safety analysis will be performed when all subjects at the site in Melbourne have completed the 3 month visit (i.e. visit 6). Based on the result of this interim analysis a ‘go/no go’ decision will be taken if to proceed with the investigation at the other sites. Focus of this safety analysis will be on reported Serious Adverse Event (SAEs) and Adverse Event of Special Interest (AESIs), i.e.:

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

The ’go/no go’ decision will be taken by the co-ordinating investigator and the Sponsor in collaboration with the principal investigator at the Melbourne site

10.10 Statistical Analysis Plan

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

11 STATEMENT OF COMPLIANCE

11.1 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 and institutional review board.

The investigation shall not begin until approval/favourable opinion from ethics committee (EC) and institutional review board (IRB) has been obtained.

11.2 Regulatory requirements for the conduct of the investigation

The investigation involves devices that are not regulatory approved in the EU or US, (not received CE mark or 510k clearance/PMA approval), therefore the investigation needs approval from regulatory authorities within EU and from FDA in the US.

The investigation shall not begin until approval/favourable opinion from the regulatory authorities has been obtained.

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

11.3 Updates

The appropriate ethics committees, institutional review board and competent authorities shall after initial approval of the investigation receive the following information:

- Status reports and written summary of the investigation as required
- 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 committees, institutional review board and competent authorities.

11.4 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[19].

In the US, the FDA recognises ISO 14155:2011 with the following exceptions:

- Sections 4.5.2-5, 7.1.2: Institutional review board membership and procedures must follow US regulations
- Sections 4.7.3.4, 4.7.4-5: Informed consent content and procedures must follow US regulations
- Sections 6.4.1, 8.2.4.5.j-k, 8.2.5, 9.7-8. Annex A.14, Annex F: Adverse event reporting procedures must be consistent with US regulations

12 ADMINISTRATIVE ASPECTS

12.1 Training

The Sponsor will organise an initiation visit where 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 running the investigation at the site will be discussed with the investigators and queries clarified.

The principal investigator will ensure that appropriate training relevant to the 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.

Each Investigator performing the surgery in the clinical investigation will be trained in the surgical procedures for the investigational device.

12.2 Investigational data

12.2.1 Case report form

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

12.2.2 Source data

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/monitor complete the template ‘Origin of source data’ stipulating where source data should be recorded at the investigational site.

12.2.3 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.

12.3 Archiving

The Sponsor and Principal investigator shall maintain the investigation documents as required by the applicable regulatory requirements.

12.4 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 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 investigational devices

12.5 Quality control

12.5.1 Monitoring

The Sponsor will work in collaboration with a Contract Research Organisation (CRO) that will appoint a monitor that will visit sites during the investigation. The Sponsor will ensure that monitor will be appropriately trained and informed about the nature of the investigation. The CRO will ensure that the monitor will be appropriately training according to ISO standard[19] 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 CRF.

The monitor must have direct access to source data.

12.5.2 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 standard[19] and applicable regulatory requirements.

12.5.3 Sponsor expertise

Sponsor representatives such as engineers or regional staff shall be present at each site during first surgery and first fitting of the Osia™ Sound Processor to provide technical expertise to the study team. The patient´s name or identifying details should not be disclosed.

12.6 Clinical Investigation Plan

12.6.1 CIP amendment

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

12.6.2 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 as soon as possible and to the EC/IRB and Competent Authority according to local regulation.

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 and institutional review board and regulatory authorities will be informed of any significant protocol deviations.

12.7 Suspension or premature termination

The sponsor may suspend or prematurely terminate either an individual investigation site or the entire clinical investigation for significant and documented reasons. A Principal investigator may suspend or prematurely terminate participation in the clinical investigation at the investigation site for which he/she 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.

12.8 Publication policy

The result of this clinical investigation 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 clinical investigation 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.

12.9 Timetable

First subject first visit	Q1/Q2 2017
Last subject first visit	Q2/Q3 2018
Last subject last visit	Q2/Q3 2019

12.10 Definition of end of investigation

End of investigation is defined as 'last subject last visit.

13 BIBLIOGRAPHY

1. Briggs R, Van Hasselt A, Luntz M, Goycoolea M, Wigren S, Weber P, Smeds H, Flynn M, Cowan R. Clinical performance of a new magnetic bone conduction hearing implant system: results from a prospective, multicenter, clinical investigation. Otol Neurotol. 2015 Jun;36(5):834-41.

2. Den Besten CA, Stalfors J, Wigren S, Ivarsson Blechert J, Flynn M, Eeg-Olofsson M, Aggarwal R, Green K, Nelissen RC, Mylanus EAM, Hol MKS. Stability, survival and tolerability of an auditory osseointegrated implant for bone conduction hearing: long term follow-up of a randomized controlled trial. Otol Neurotol. 2016 *(Accepted, in print)*

3. Nelissen RC, Stalfors J, de Wolf MJ, Flynn MC, Wigren S, Eeg-Olofsson M, Green K, Rothera MP, Mylanus EA, Hol MK. Long-term stability, survival, and tolerability of a novel osseointegrated implant for bone conduction hearing: 3-year data from a multicenter, randomized, controlled, clinical investigation. Otol Neurotol. 2014 Sep;35(8):1486-91.

4. P1114536 - Osia Sound Processor user manual

5. P1114535 - OSI100 Implant Physician's Guide

6. P893137, OSI100 Implant Surgical Instrument Sterilisation Reprocessing Guide

7. P773697, Osia Fitting Software User Guide

8. P803354 Baha Fitting Software - CSDS (Download) or P803254 Baha Fitting

9. D800778 – Clinical Investigation Report CBAS5439, 12 Months clinical, 1.B

10. Osia Intraoperative Test Software 1.0 User Guide

11. ISO 8253-1 2010

12. 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. International Journ.of Audiol.2013 52(6), 409-12

13. D784107, Post Market Surveillance Report, Baha Attract, November 2015

14. D788296, Post Market Surveillance Report, Baha Connect, November 2015)

15. D769711, Literature Search and Evaluation: Protocol and Report. Baha Attract System

16. 411167, Clinical Evaluation Report Nucleus CI24RE Cochlear Implants

17. D701349, Post Market Surveillance Report, Codacs DI110 implant and DF110 Fixation system

18. D893156 OSI100 Implant MRI Guidelines

19. ISO 14155:2011

APPENDIX 1 - NEW ATB SPECIFIC INSTRUMENTS AND TEMPLATE

1. 

Actuator template. Used to ensure the actuator is positioned correctly and the lead exit placed properly. Reusable instrument.

2. 

Clearance indicator. Used to ensure there is adequate clearance for the actuator above the level of bone. Reusable instrument.

3. 

OSI100 Recess checking gauge. Used to mark the bone recess on the skull, and measure the depth of the bone recess after drilling. Reusable instrument.

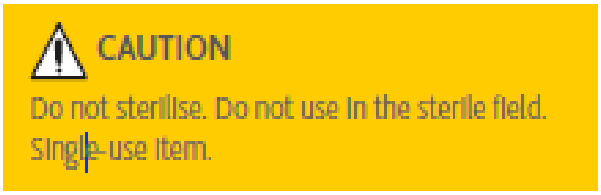
4. 

Guide Pin, Attaches to the BI300 implant. Provides an attachment point
for the Clearance indicator , Actuator Template and Isolator. Single use instrument.

5. 

OSI100 template. Silicon template of the entire implant to be used inside the **sterile field**. Single use item.

6. 



OSI100 Non sterile template. Used to determine, or check, the optimum implant position and mark it **onto the skin before incision**. Single use item.

14 APPENDIX 2 - SUPPORTIVE AND SURGICAL NON-INVESTIGATIONAL DEVICES USED IN THE INVESTIGATION

Product	**Article name**	**Sterile/ non-sterile**	**Single/ re-usable**	**Regulatory approved**
	Surgical tools			
90469	Screwdriver Unigrip 95mm	Non sterile	Reusable	Yes
92143	Multi wrench with ISO adapter	Non sterile	Reusable	Yes
90381	Machine Screwdriver Unigrip 25mm	Non sterile	Reusable	Yes
92142	Implant inserter	Non sterile	Reusable	Yes
91116	Drill indicator	Non sterile	Reusable	Yes
95070	Soft tissue gauge 6 mm	Non sterile	Reusable	Yes
93363	Conical guide drill 3+4 mm	Sterile	Single use	Yes
92140	Widening drill 3mm	Sterile	Single use	Yes
92141	Widening drill 4mm	Sterile	Single use	Yes
Z60479	Bone Recess Template	Non sterile	Reusable	Yes
Z33017	Array Exit Marking Template	Non sterile	Reusable	Yes
P772551	Actuator Template	Non sterile	Reusable	No
P772552	Clearance indicator	Non sterile	Reusable	No
P795943	OSI100 Recess checking gauge	Non sterile	Reusable	No
Z496667	OSI100 Single use kit: Guide Pin, OSI100 templ.	Sterile	Single use	No
Z60479	Bone Recess template	Non sterile	Reusable	Yes
P794316	OSI100 template (Non sterile, single use)	Non sterile	Single use	No
90944	Raspatorium	Non sterile	Reusable	Yes
90943	Dissector	Non sterile	Reusable	Yes
93339	Baha Ruler	Non sterile	Reusable	Yes
	Supportive items			
P783571	Osia™ Fitting Software CSDS Clin Trial (version 1.0.2)	NA	Reusable	No
N/A	Baha Fitting Software – CSDS (Download)	N/A	Reusable	Yes
P803254	Baha Fitting Software version 4.0 SR2	NA	Reusable	Yes
B13033	BATTERY ZN AIR P675 IMPLANT PLUS	Non-sterile	Single use	Yes

CBAS5539 CIP Version 5

Z60686	Freedom Programming Pod	Non-sterile	Reusable	Yes
Z327114	Cochlear Nucleus Programming Shoe with Cable	Non sterile	Reusable	Yes
Z544308	CP950 Programming Shoe Adaptor Cable Kit	Non sterile	Reusable	Yes
Z22502	Signal Check wand	Non sterile	Reusable	Yes
D1132381	Osia™ Intraoperative Test Software CSDS Clin Trial (version 1.0.1)	N/A	Reusable	No
92841	Cochlear Baha BP110 Power Sound Processor	N/A	Reusable	Yes
95750	Baha Softband	N/A	Reusable	Yes
P793402	Cochlear Softwear Pad (5pcs)	Non-sterile	Single use	Yes
P993402	Baha SoftWear Pad (15pcs)	Non-sterile	Single use	Yes