Clinical Investigation Plan (CIP)

Early experience of a new implant system for bone conduction hearing in the pediatric population.

Protocol Number	CAM5706
Version	CONFIDENTIAL DRAFT
Date	August 30, 2017
Sponsor	Cochlear Americas 13059 E. Peakview Ave., Centennial, CO 80111 USA

INVESTIGATOR RESPONSIBILITIES

I, the undersigned, am responsible for the conduct of the study at the site below and by my signature below, I confirm that I have read, understand, and will strictly adhere to the study protocol, “Early experience of a new implant system for bone conduction hearing in the pediatric population.”

Clinical Investigational Site

Primary Investigator’s Name (print)

Title

Signature

Sponsor Representative

Title

Signature

INVESTIGATIONAL SITES

Principal Investigator	[redacted]

CLINICAL INVESTIGATION MANAGEMENT

Study Manager	[redacted]

SYNOPSIS

Name of Sponsor	Cochlear Americas
Protocol number	CAM5706
Investigational title	Early experience of a new implant system for bone conduction hearing in the pediatric population.
Design	Open, prospective, single center clinical investigation.
Investigational device(s)	ATB System (Osseointegrated Steady State Implant System, commercially to be named Osia™ System).
Aim for conducting the investigation	The aim of the investigation is to collect safety information on children and adolescents implanted with the ATB System.
Inclusion criteria	Individuals 5 through 18 years of age who have: • 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. • Subject does not benefit from or will not wear a conventional hearing aid Note: Candidates include individuals seeking new implantation unilaterally (in one ear) or bilaterally (both ears) as well as individuals already implanted with a bone-anchored device seeking a second-side implant. **OR** • Single-sided sensorineural deafness and a candidate for Baha surgery. • Air conduction thresholds with a pure-tone average (PTA4; mean of 0.5, 1, 2, and 3 kHz) of ≤ 20 dB HL in the good ear. • . Subject does not benefit from or will not wear a conventional hearing aid.

Exclusion criteria	• Uncontrolled diabetes as judged by the investigator. • Subject who has received radiotherapy in the area of implantation, or such radiotherapy is planned during the study period. • Current use of ototoxic drugs. • Condition that could jeopardize osseointegration and/or wound healing 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, as determined by the surgeon. • Unable to follow investigational procedures. • Participation in another clinical investigation with pharmaceutical and/or device.
Number of subjects	Up to 20 subjects
Duration of subjects participation	12 months
Number of sites	1

OBJECTIVES AND OUTCOME MEASURES

Primary objective	Outcome measure
To quantify the type and severity of adverse events in the pediatric population implanted with the Osia system.	Information will be collected from visit 2 through visit 7 of the trial.

Secondary objectives	Outcome measures
To collect surgical information.	• Soft tissue thickness • Soft tissue reduction performed • Type of anesthesia • Surgery time • Bone polishing/removal at the actuator site • BI300 Implant length • Location of BI300 Implant • Surgical incision type/location
To collect information about daily use of sound processor (dependent on child's ability to report).	• Daily usage time • SoftWear Pad use • Choice of magnet strength
To compare the self-reported assessments of hearing outcome with the Investigational device and in a preoperative hearing situation.	• Speech, Spatial and Qualities of Hearing Scale -12 (SSQ-12) using the investigational device at 6 months postoperatively vs. the unaided condition preoperatively. • For children unable to complete the SSQ-12: Speech Spatial Questionnaire for Parents using the investigational device at 6 months postoperatively vs. the unaided condition preoperatively.

ANCILLARY OBJECTIVES AND MEASURES

Ancillary measures are additional measures that will be captured only if the child is capable of completing or performing the evaluation as determined by the Investigator.

Ancillary objective	Outcome measures
To compare unaided hearing performance to aided hearing performance using the investigational device.	**Audiometric:** Free-field thresholds (PTA4; mean of 0.5, 1, 2, and 4 kHz) using the investigational device at 6 months postoperatively vs. the unaided condition preoperatively. **Speech Perception:** Aided monosyllabic words in quiet (% correctly perceived words at 60 dB SPL) using the investigational device at 6 months postoperatively vs. the unaided condition preoperatively.

STUDY TEST SCHEDULE

Visit	1 Preop	2 Surgery	3 Post-op Follow Up	4 Fitting	5	6	7
Visit time point		**0**	**2W**	**4W**	**3M**	**6M**	**12M**
Visit window			**± 5D**	**± 1W**	**± 2W**	**± 3W**	**± 4W**
Demographics	X						
Medical history	X						
Baseline characteristics	X						
Eligibility criteria	X						
Informed consent	X						
Soft tissue thickness		X					
Surgery		X					
IOTS		X					
Post-op follow up			X				
Sound processor fitting				X			
Magnet choice				X	X	X	X
Audiogram	X			X[2]	X[2]	X[2]	X[2]
Free-field thresholds[1]	X			X	X	X	X
Speech recognition[1]	X			X	X	X	X
Patient reported outcomes	X					X	X
Daily use					X	X	X
Device deficiency		X	X	X	X	X	X
Adverse events		X	X	X	X	X	X
Concomitant medication or treatment		X	X	X	X	X	X
Extra visits	As needed						

1 These measures are ancillary, dependent on the child's capability to complete the tests. If captured, measures will take place in the unaided condition preoperatively and in the aided condition, using the investigational system, postoperatively.

2 Bone conduction only.

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LIST OF APPENDICES

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1	New ATB specific instruments and templates.
2	Other devices used in the investigation, non-investigational.

ABBREVIATIONS

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
CI	Cochlear Implants
CIP	Clinical Investigation Plan
Codacs	Cochlear® Direct Acoustic Cochlear Stimulator
EC	Ethic Committee
eCRF	Electronic Case Report Form
FS	Fitting Software
IFU	Instruction For Use
IOTS	Intraoperative Test System
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 Organization
PP	Per Protocol
USADE	Unanticipated Serious Adverse Device Effect

1 INTRODUCTION

1.1 Background

1.1.1 The Baha System

The Cochlear™ Baha® bone conduction system 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 whereas, the passive Baha Attract System uses a *magnetic* connection through intact skin.

Magnetic conduction has the advantage over skin-penetrating systems of eliminating daily cleaning, reduction in reported adverse skin reactions of the implant site and has been perceived as more cosmetically appealing by potential candidates. The skin-penetrating abutment of the traditional Baha System has been seen as a barrier for many candidates. The passive Baha Attract System incorporates both internal 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 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 Osia System

The Osia System (Osseointegrated Steady State Implant System) has been 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 Osia 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 Osia System, it will also be possible to position the transducer closer to the ear canal, which may further improve audiological outcomes to include better speech perception.

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

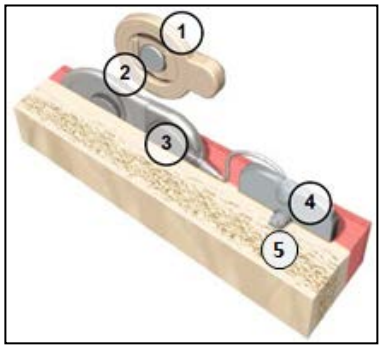

Figure 2: The ATB System.

The Osia 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 an electric analog 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 through the osseointegrated BI300 Implant (5).

With the Osia 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 Osia System that combines aesthetics with higher performance to meet the needs of subjects with mixed hearing loss. The target fitting range is up to 55 dB HL 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 primary aim of the investigation is to collect preliminary safety and efficacy information on children and adolescents who present with conductive or mixed hearing loss or single-sided sensorineural deafness (SSD) and are implanted with the Osia System.

1.3 Investigational device

1.3.1 Description of the investigational device

The Osia 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 Osia System has a fitting range of up to 55 dB HL SNHL, and shall be implanted and fitted unilaterally in this clinical investigation.

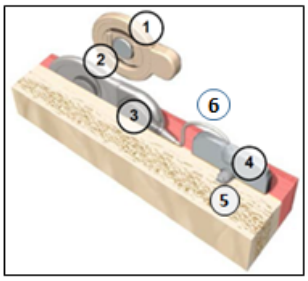

Figure 3: The ATB System parts. 1. Sound Processor, 2. Receiver, 3. Stimulator, 4. Actuator, 5. BI300 Implant, 6. Lead.

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

- Osia Sound Processor (SP) (1): The sound processor consists of an all-in-one off-the-ear processor that includes: an active coil, magnet (with seven possible strengths), and two battery cells. The SP has identical hardware as the commercially approved Nucleus CP950 Sound Processor for cochlear implants, but with Osia specific firmware.

  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 that 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 Osia SP is found in the Osia Sound Processor User Manual [4].

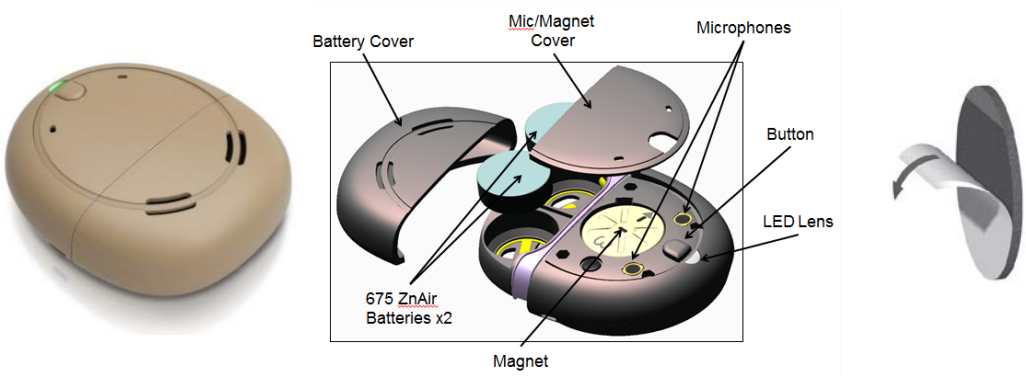

Figure 4: Left: Osia Sound Processor, external view (upper surface). Middle: Osia Sound Processor, partially exploded view. Right: SoftWear™ Pad, showing removal of protective film to expose self-adhesive surface.

- 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[1] also use identical coil, magnet, and case. A magnet located at the center 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 Osia specific electronics, which is powered by two batteries in the external sound processor. The receiver-stimulator is completely over-molded by a silicone coating.

- Actuator (4): The 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 Osia Actuator are over-molded by a silicone coating (Figure 5).

[1] The CE-marked Codacs system refers to the Cochlear Direct Acoustic Stimulator, implant technology not commercially available in the U.S.

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 1.6.4.

- 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-molded by a silicone coating.

- BI300 Implant (5): The Osia 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 comes in two different lengths, 4mm and 3 mm and is made of titanium. The surface is moderately roughened (TiOblast™) on its intraosseous parts.

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

Table 1: List of investigational device components.

Name	Description	Part Number
Osia™ Sound Processor	Sandy Blonde Chocolate Brown Slate Grey Black	P798644 – P798667
Osia Implant	Receiver-Stimulator Actuator Lead	Z398787
CP950 Magnets	Strength from 0.5 – 6	Z566412, Z502922, Z502923, Z502924, Z502925, Z566414, Z566415
BI300 Implant	4 mm, 3 mm	92129, 92128

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

1.3.2 Manufacturer of investigational device(s)

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

1.4 Description of comparator

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

1.5 Blinding

No blinding will be used in this clinical investigation.

1.6 Other devices used in the investigation, non-investigational

1.6.1 Surgical instruments

The surgical procedure for the Osia 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 Nucleus CI24RE cochlear implant. Hence, Osia 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 Osia System. Table 2 lists the recommended surgical instruments for Osia surgery. The Osia specific surgical instruments used to prepare the bone bed for the Osia 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 Osia Actuator compared to Baha Attract implant magnet (rectangular versus circular).

Table 2: Osia surgical instruments.

Instrument	Description	Part Number
Osia specific Reusable Instruments	Actuator Template	P772551
	Clearance indicator	P772552
	OSI100 Recess checking gauge	P795943
Osia specific Single Use Instruments	OSI100 Single use kit (Sterile, single use) Includes: Guide Pin, OSI100 template	Z496667
	OSI100 template (Non sterile, single use)	P794316

Instrument	Description	Part Number
Cochlear Baha Reusable Instruments	Screwdriver Unigrip 95mm	90469
	Multi wrench with ISO adapter	92143
	Machine Screwdriver Unigrip 25 mm	90381
	Implant inserter	92142
	Drill indicator	91116
	Soft tissue gauge 6 mm	95070
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 Osia specific instruments and templates are found in **Appendix 1.** Complete information for the Osia surgical instruments is found in the professional guides [5, 6]. Also, see **Appendix 2** for a list non-investigational instruments, and supportive items.

1.6.2 Fitting Software (FS)

The investigator shall use the Osia Fitting Software (OFS) to configure the operational features of the Osia Sound Processor for each subject at visit 4. Communication between the fitting software and the sound processor is achieved using a 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.

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

1.6.3 Programming pod

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

1.6.4 Intraoperative test system

An intraoperative test system (IOTS) will be available to confirm device integrity at the time of implantation. An intraoperative test system is available and in use for Cochlear Implants (CI) and Codacs to verify the functionality. For the Osia System, the IOTS will

evaluate any potential damage 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.

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

Figure 6: Intraoperative Test System (IOTS) concept.

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, 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 6)). The test also relies on the use of a custom silicone Isolator to provide mechanical isolation for the actuator during the test (Figure 7). 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.

Figure 7: ATB Implant, with actuator pre-mounted onto the Isolator.

1.6.4.1 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 • Programming Pod • Osia Intraoperative Test Software • 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

1.7 Treatment after the completion of the investigation

After the clinical investigation, the subjects will be able to continue with their investigational device (Osia 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 Osia Implant is expected to have a lifetime of at least 10 years. Any changes to the implant during or after this time-period should be performed according to the implant revision/replacement procedure described in the professional guide [5].

Future upgrades of the Osia Sound Processor, used together with the implant in this clinical investigation, may be possible.

2 SUBJECTS AND SUBJECT PROTECTION

2.1 Selection of Subjects

2.1.1 Inclusion criteria

Individuals 5 through 18 years of age will be eligible for inclusion in the investigation if **all** of the criteria below are met:

- 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.
- Subject does not benefit from or will not wear a conventional hearing aid.

Note: Candidates may include individuals seeking new implantation unilaterally (in one ear) or bilaterally (both ears) as well as individuals already implanted with a bone-anchored device seeking a second-side implant.

OR

- Single-sided sensorineural deafness who is a candidate for Baha surgery.
    - Air conduction thresholds with a pure-tone average (PTA4; mean of 0.5, 1, 2, and 3 kHz) of ≤ 20 dB HL in the good ear.
- Subject does not benefit from or will not wear a conventional hearing aid.

2.1.2 Exclusion criteria

- Uncontrolled diabetes as judged by the investigator.
- Subject who has received radiotherapy in the area of implantation, or such radiotherapy is planned during the study period.
- Current use of ototoxic drugs.
- Condition that could jeopardize osseointegration and/or wound healing 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, as determined by the surgeon.
- Unable to follow investigational procedures.
- Participation in another clinical investigation with pharmaceutical and/or device.

2.2 Number of subjects

Up to 20 subjects will be recruited for this study at 1 investigational site.

2.3 Duration of subject participation

Subjects will participate in a 12-month protocol in total.

2.4 Subject enrolment and informed consent/assent

As part of the informed consent and/or assent process, an investigator must explain the following to the potential investigational subject and/or the parent or legal guardian:

- The rationale, aims, and objectives of the investigation.
- Risks and benefits.
- Alternative treatments.
- Extent of the subject's involvement.
- That the subject can withdraw from the study at any time.
- That the confidentiality of patient data will be maintained at all times.
- That the subject and/or parent/legal guardian will be informed if new information becomes available that may be relevant to continued, willing participation in the trial.

The subject and/or parent/legal guardian must be provided the opportunity to ask any questions he/she/they might have. Signed and dated informed consent and/or assent must be obtained before any investigational procedure can be performed. A copy of the Informed Consent/Assent Forms shall be given to the subject and parent/legal guardian, when applicable.

The Sponsor and the Investigator(s) shall avoid improper influence on or inducement of the subject, monitor, the Investigator(s), or other parties participating in or contributing to the clinical investigation.

2.5 Subject Identification

To maintain confidentiality, the subject's name will not be recorded on any study document other than the informed consent form. All individuals who provide informed consent (sign the informed consent form) are considered consented into the study and will be assigned a unique identifier. A unique alphanumeric code will identify the subject throughout the course of the study. For example, CA01-OSI-0000, where:

- CA = Canada

- 01 = a sequential numeral corresponding the order in which a subject is enrolled into the study for a given study site, in this case this would correspond to the first subject recruited into the study for a particular site,
- OSI = an abbreviation for the study,
- 0000 = a unique, numeric study site identification.

2.6 Randomization

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

2.7 Completed Subjects

Each subject in the study will be considered completed when all assessments through 12 months postactivation have been performed in accordance with the study protocol. To be considered a primary endpoint success, subjects must retain their originally implanted device through the 6 month visit.

2.8 Discontinued Subjects

Any subject may voluntarily discontinue the study at any time without prejudice. The Investigator may discontinue a subject from the study at any time if (s)he considers that remaining in the study compromises the subject's health or the subject is not sufficiently cooperative. In either event, reason(s) for discontinuation should be recorded on a study withdrawal form, provided as part of the CRFs for the study.

Possible reasons for study discontinuation include the following:

- AE necessitating discontinuation from the study.
- The subject is lost to follow-up.
- Voluntary decision to withdraw consent made by the subject[2].
- Investigator decision[3].
- Other reason.

In case of a subject lost-to-follow-up, the Investigator must attempt to contact the subject (or relative/family contact) by phone, email or letter at least three times. If attempts are unsuccessful, the 'subject withdrawal' form is to be completed in the study file and reported, as appropriate, in required reports to the Sponsor, Ethics and Health Canada.

[2] Withdrawal of consent is defined as the subject's voluntary decision to revoke consent to continue participation in the study.

[3] Subject withdrawal from the study is defined as an Investigator decision. The Investigator may elect to withdraw a subject from the study at any time if he/she considers that remaining in the study compromises the patient's health or if the Investigator considers the subject lost to follow-up.

2.9 Premature Study Termination

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.
- The may be other reasons 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.

2.10 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 up to 20 evaluable subjects.

3 DESIGN OF THE CLINICAL INVESTIGATION

This clinical investigation is an open, prospective, single center clinical investigation with a duration of 12 months. Performance for each subject at 6 months postoperative will be compared to his/her own preoperative unaided hearing situation.

3.1 Justification for the design of the clinical investigation

The primary intent for this study involves the collection of preliminary safety and efficacy information on children, 5 through 18 years, implanted with the Osia system.

3.2 Objectives and outcome measures

Primary objective	Outcome measure
To quantify the type and severity of adverse events in the pediatric population implanted with the Osia system.	Information will be collected from visit 2 through visit 7 of the trial.

Secondary objectives	Outcome measures
To collect surgical information.	• Soft tissue thickness • Soft tissue reduction performed • Type of anesthesia • Surgery time • Bone polishing/removal at the actuator site • BI300 Implant length • Location of BI300 Implant • Surgical incision type/location
To collect information about daily use of sound processor (dependent on child's ability to report).	• Daily usage time • SoftWear Pad use • Choice of magnet strength
To compare the self-reported assessments of hearing outcome with the investigational device and in a preoperative hearing situation.	• Speech, Spatial and Qualities of Hearing Scale -12 (SSQ-12) using the investigational device at 6 months postoperatively vs. the unaided condition preoperatively. • For children unable to complete the SSQ-12: Speech Spatial Questionnaire for Parents using the investigational device at 6 months postoperatively vs. the unaided condition preoperatively.

3.2.1 Ancillary Objectives and Measures

Ancillary measures are additional measures that will be captured only if the child is capable of completing or performing the evaluation as determined by the Investigator.

Ancillary objective	Outcome measures
To compare unaided hearing performance preoperatively to aided hearing performance using the investigational device postoperatively	**Audiometric:** Free-field thresholds (PTA4; mean of 0.5, 1, 2, and 4 kHz) using the investigational device at 6 months postoperatively vs. the unaided condition preoperatively. **Speech Perception:** Aided monosyllabic words in quiet (% correctly perceived words at 60 dBA) using the investigational device at 6 months postoperatively vs. the unaided condition preoperatively.

4 PROCEDURES

Procedures performed during the clinical investigation are outlined in the flow chart, under **Study Test Schedule**.

4.1 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 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.

4.2 Demographics

The following demographic data will be recorded at visit 1:

- Age collected as date of birth (month and year).
- Gender.
- Ethnicity.
- Nicotine use, if applicable.

4.3 Medical history

The following information will be recorded at visit 1:

- Relevant medical and surgical treatment as judged by the investigator.
- Current concomitant medication and treatments.

4.4 Baseline characteristics

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

- Treatment ear (indicate left or right).
- Type of hearing loss: (Conductive, Mixed, or SSD).
- Etiology: (chronic) infection, tumor, trauma, otosclerosis, unknown.
- Current hearing aid (yes/no, specify model, side and years of hearing aid use, reason for change).
- Previous experience from amplified sound through a non-surgical solution (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).

4.5 Preoperative Audiometric Assessments

Preoperative 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 is acceptable, as long as it has been completed during the last 6 months, and contains all the required frequencies (minimally air and bone conduction at 500, 1000, 2000, and 4000 Hz) per protocol. The subject's pre-operative PTA4 (pure-tone average of 500, 1000, 2000, and 4000 Hz) should be computed and recorded to ensure the subject meets the inclusion criteria.

If an audiogram is older than 6 months and/or does not contain required frequencies, an entirely new audiogram should be performed at visit 1. Contralateral masking should be used, if needed, according to local practice. The hearing care professional shall always record the unmasked threshold and record the masked threshold, if applicable.

4.6 Soft tissue thickness

At visit 2 (start of surgery) soft tissue thickness should be measured. For the Osia System, the skin thickness should not exceed 6 mm to ensure optimal retention and

system performance. The measurement should be performed in the center of the marked coil position. For complete instruction, see the surgery guide [5].

4.7 Surgery

The surgery is performed at visit 2. 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 and last suture).
- Bone polishing/removal at the actuator site (yes/no).
- BI300 Implant length (3 mm/4 mm).
- Location of BI300 Implant (mm from the ear channel).
- Type of anesthesia (general/local/conscious sedation).
- 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.

4.8 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 laptop provided by the Sponsor. The software collects data from the transducer of the implant and will assist understanding of the behavior and performance of the transducer once implanted on a recipient. IOTS data will be saved on the laptop until study is ended when it will be transferred to the Sponsor in a coded way.

4.9 Sound Processor fitting

The Osia Fitting Software [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. The fitting software will be installed on a laptop provided by the Sponsor, and the fitting-data will be saved on the laptop until study is ended when it will be transferred to the Sponsor in a coded way.

4.10 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, ranging 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 subject preference.

5 ASSESSMENTS

Assessments, including ancillary measures that will be performed during the clinical investigation are shown in the flow chart, under **Study Test Schedule**.

During the assessments with the study device, the signal processing of the sound processors will be harmonized according to given instructions given in the CRF. This will also be included in the staff training at each participating center during the site initiations.

5.1 Postoperative Audiometric Assessment

Bone conduction thresholds for the study ear will be monitored, to characterize observed unaided thresholds postoperatively. Appropriate masking should be used, if needed, according to local practice. Recognizing that a pediatric subject may not be able to complete measures at all frequencies, minimally thresholds at 500, 1000, 2000, and 4000Hz need to be captured for the study ear.

5.2 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 the standard SSQ [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-12 questionnaire at visits 1, 6, and 7.

- At visit 1, the subjects shall complete the SSQ-12 questionnaire prior to testing and shall be answered with respect to an unaided hearing situation, even for subjects with a previous hearing device.

- At visits 6 and 7, the subjects shall complete the questionnaire for the aided situation (with the investigational device).

In the event the subject cannot self-report on the SSQ-12, the SSQ for Parents will be deployed.

5.3 Daily use

During the clinical investigation, data regarding daily use of the sound processor will be collected.

- Average hours of daily use (hours/day) during the last month before visits 5-7.

- SoftWear Pad use (Yes/No) and frequency of change. The number of times the subject changed the SoftWear Pad between study visits.

5.4 Ancillary Assessments

The following measures are ancillary, dependent on the child's capability to complete the tests. If captured, measures will take place in the unaided condition preoperatively, at visit 1, and in the aided condition, using the Osia system, postoperatively.

5.4.1 Free-field thresholds

The purpose of this assessment is to establish hearing thresholds in the free-field through a speaker in the front position (0° azimuth) according to the so-called ascending or modified Hughson-Westlake method (Figure 8). The test shall be performed with the non-test ear blocked (in the 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. Recognizing that a pediatric subject may not be able to complete measures at all frequencies, minimally thresholds at 500, 1000, 2000, and 4000Hz need to be captured.

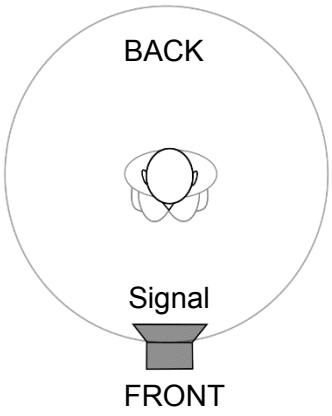

Figure 8: Free-field front speaker position.

5.4.2 Speech recognition in quiet

The purpose of this assessment is to establish the test subject's monosyllabic word recognition in quiet. The test shall be performed at 60 dB SPL using words presented in the free-field through a speaker located in front of the listener, at 0° azimuth (Figure 8). Scores shall be recorded as the percentage of words correctly identified. The test shall be performed with the non-test ear blocked (in cases of normal or near-normal hearing or a large asymmetry with the non-test ear having significantly better hearing thresholds).

6 ADVERSE EVENT AND DEVICE DEFICIENCIES

6.1 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).

6.2 Adverse Events (AE)

6.2.1 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 the Sponsor 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. c. A life-threatening illness or injury. d. A permanent impairment of a body structure or a body function. e. Led to unplanned in-patient or prolonged hospitalization. f. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function. g. Led to fetal distress, fetal death or a congenital abnormality or birth defect. **NOTE:** Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect, which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report.

6.2.2 Adverse Events

An Adverse Event is the development of an untoward medical occurrence or the deterioration of a pre-existing medical condition following or during exposure to an investigational product, whether or not considered causally related to the product or the surgical procedure to implant it. An untoward medical condition can be symptoms (e.g., nausea), signs (e.g., tachycardia, fever) or clinically significant abnormal results of an investigation (e.g., laboratory findings, chest x-ray).

Adverse events that occur during this study may be associated with the implant procedure, including adverse effects from general anesthesia, or specifically associated with the use of the device. An adverse event will be considered to be device-related when, in the judgment of the Primary Investigator, there is a logical connection between the use of the device and the occurrence of the event, above and beyond the study procedure itself.

6.2.3 Adverse Events of Special Interest (Osia Clinical Study only)

The following AEs are defined as adverse events of special interest (AESIs) and should be reported as soon as possible:

- AE that interferes 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.

6.2.4 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.

6.2.5 Serious Adverse Events

A Serious Adverse Event (SAE) is any untoward medical occurrence which:

- Results in death;
- Is life-threatening;
- Requires in-patient hospitalization for > 24 hours or prolongation of hospitalization which is not specifically required by the protocol;
- Results in permanent impairment of a body function or permanent damage to a body structure; or
- Requires medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

6.2.6 Unanticipated Adverse Device Effect

An unanticipated adverse device effect (UADE) is “any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects” [FDA 21 CFR 812.3(s)]. The Sponsor will promptly conduct an investigation upon notification by an Investigator of a UADE. The competent authority, all reviewing Ethic Committees and participating Investigators will be notified within 10 working days after the sponsor first receives notice of the effect. Thereafter, the Sponsor will submit such additional reports concerning the effect as requested.

For the purposes of this study, only unanticipated adverse device effects will be reported promptly following occurrence. Annual progress reports will contain information regarding SAE/AE occurrences.

6.2.7 Assessment and Reporting of Adverse Events

6.2.7.1 Investigator’s Responsibilities

Throughout the course of the study, all efforts will be made by the Investigators to remain alert to possible AEs. The first concern will be the safety and welfare of the subject and for providing appropriate medical intervention, as indicated. Detailed information regarding adverse events (AEs) will be recorded by the Investigator at the time an adverse event occurs using CRFs for the study. All adverse events will be recorded from the day of enrollment (Day 0) to termination of study, approval of the product, or when the subject exits the study, whichever is the last, even if the event was acknowledged as a risk factor in the *Informed Consent Form*.

AEs will be recorded on the CRF will include the following information:

- Date of onset
- Date reported to the clinic
- Description of the AE
- Seriousness
- Investigator’s assessment of the relationship of the AE to the device and/or procedure
- Treatment
- Outcome

6.2.7.1.1 Adverse Event Follow-up

All AEs must be followed until resolution, or the condition stabilizes. The Investigator is responsible to ensure that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as possible the nature and/or causality of the AE. This may include additional laboratory tests or investigations, or consultation with other health care professionals. Cochlear or its designee may request that the Investigator perform or arrange for the conduct of supplemental measurements and/or evaluations. AE follow up information will be recorded using the CRFs for the study.

6.2.7.2 Sponsor's Responsibilities

All AEs will be reported annually to competent authorities in accordance with local regulations. All unanticipated adverse device effects (UADEs) will be reported within 10 calendar days of the event. Cochlear Americas or its designee will notify all participating Investigators of any new information that alters the current risk-benefit assessment of the study device or that would be sufficient to consider changes in management of the Nucleus cochlear implant or in the overall conduct of the trial.

6.3 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.

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

7.1 Anticipated clinical benefits

The Osia 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 Osia System may provide additional advantages as it combines benefits from both a percutaneous (skin-penetrating) and transcutaneous Baha system.

The Osia 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 Osia 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, it is expected that efficiency of sound transmission will be on a par with a percutaneous system.

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

The Osia System, like the Baha Attract System, may significantly reduce the risk of implant site infections, and eliminate the need for daily maintenance care**.** For the transcutaneous Baha Attract System and Osia 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 Osia System may 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 System[15].

7.2 Anticipated adverse device effects

Just like any surgical treatment, Osia surgery is not free of risks. Risks associated with the implantation and use of the Osia System cannot be completely eliminated. General risks associated with surgery under general or local anesthesia 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 the Osia 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].

Postmarket surveillance information is collected and those findings relevant for the Osia System is presented below:

7.2.1 Osia Sound Processor

The Osia SP has identical hardware as the CP950 Sound Processor for Cochlear Implants, but with Osia 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 possible but not reported as a serious problem and often solved by adjusting the magnet strength. Potential skin irritation problems will be managed by a combination of adjustment of magnet strength and/or use of the Softwear Pad.

7.2.2 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 the 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. 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].

7.2.3 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].

7.2.4 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 Osia 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].

7.2.5 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].

7.3 Risks associated with participation in the clinical investigation

Risks associated with participation in this study are anticipated to be similar for a child in relation to the adult population. The investigational device incorporates several components from already FDA and Health Canada approved products. There is no guarantee that the Osia Implant will not cause any adverse device events. The Osia Implant is expected to have a lifetime of about 10 years. As with any new surgical product and medical device, there is a risk that Unanticipated Adverse Event 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 Osia Implant. The subject will then end participation in the clinical investigation and follow normal clinical care and follow-up.

7.4 Control and mitigation of risks

The surgical procedure is described in the surgery guide for the Osia 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 during the surgical validation activity.

Before the enrollment of the clinical investigation site, each participating investigator will have completed surgical training using the Osia device according to the surgery guide.

MRI examinations may be performed safely with this implanted device 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 Osia 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 Osia System will be positioned are excluded from the investigation.

7.5 Risk-to-benefit assessment

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

8 DATA ANALYSIS

All subjects who are consented into the clinical study will constitute the intention-to-treat (ITT) population for the purposes of safety evaluation. Only subjects implanted with the Osia implant will be considered as the completed cases (CC) population and per protocol (PP).

Since the primary intent of this study is to provide preliminary safety and efficacy information, no formal hypotheses or sample size estimates were derived for this study.

Demographic and outcomes data for primary, secondary, and ancillary objectives will be tabulated individually along with group summary descriptive statistics where relevant.

9 STATEMENT OF COMPLIANCE

9.1 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/favorable opinion from ethics committee (EC) and institutional review board (IRB) has been obtained.

9.2 Regulatory requirements for the conduct of the investigation

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

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

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

9.3 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.

9.4 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].'

10 ADMINISTRATIVE ASPECTS

10.1 Training

The Sponsor will organize a Site Initiation and Training 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.

10.2 Investigational data

10.2.1 Case report form

Data collection will be done using a combination of paper case report forms (CRFs) and electronic data capture (EDC) system. Specific training and instruction on how to complete the CRFs and enter the data into the EDC will be provided to the investigator and other site staff according to the delegation log. Upon request by the investigator, the Sponsor may transfer data collected on the paper CRF by the investigational site to the EDC under special circumstances such as during EDC maintenance or system updates. Completed eCRFs within the EDC will be reviewed and signed off by an investigator prior to the completion of the trial.

10.2.2 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.

10.2.3 Data management

All study data will be entered into an Electronic Database Capture (EDC) system. Study personnel requiring access will have their own Login/Password. Access to clinical study information will be based on an individual's role and responsibilities. The application

provides hierarchical user permission for data entry, viewing, and reporting options. For optimum security, all communications between the users and the EDC operate on a secured socket layer (SSL) using 256-bit encryption. The web servers are protected by a managed firewall from potential web and network attacks and the network is guarded by an intrusion detection and protection surveillance system against malicious threats.

This application is designed to be in full compliance with International Conference on Harmonization and Good Clinical Practices (ICH-GCP), FDA CFR 21 Part 11 Electronic Record and Electronic Signatures, the FDA's "Guidance: Computerized Systems Used in Clinical Trials (May 2007), and the Privacy Rule of the Health Insurance Portability and Accountability Act of 1996 (HIPAA)."

As part of the data entry and validation process, the data stored in the EDC is checked against the source data, and also against edit check queries to confirm that the data received is within expected ranges. If any data is missing or is outside of expected limits, a query is created and sent to the site coordinator so that data may be verified and corrected. All changes made to a form are stored in an audit trail.

10.2.4 Record Keeping and Retention

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

An Investigator must in reasonable time, upon request from any properly authorized officer or employee of FDA/relevant health authority or regulatory agency, permit such officer or employee to have access to requested records and reports, and copy and verify any records or reports made by the Investigator. Upon notification of a visit by a regulatory authority, the Investigator will contact the Sponsor or its designee immediately. The Investigator will also grant Sponsor representatives the same privileges offered to relevant health authority or regulatory agents/officers/employees.

The Investigator must provide the Sponsor or its designee with the following documents at the time of site qualification and prior to study initiation and retain a copy in the site study file:

- Signed and dated curriculum vitae for the Principal Investigator.
- A copy of the original approval for conducting the study by the Ethics Committee. Renewals, with continuance of the study, must be submitted at yearly intervals or as required by policy and a copy of the approved and dated renewal provided to the Sponsor.
- A copy of the approved informed consent form along with any modifications initiated by the Sponsor over the course of the study.
- An Ethics member list and Federal Wide Assurance (FWA) Number.

- A signed Financial Disclosure Form for each Investigator.
- An Investigator Agreement for this protocol signed and dated by each Investigator.

In addition to the documents listed above, the study site will also retain the following items and make them available for Sponsor review upon request.

- Certifications, applicable study equipment (audiometers, etc.) calibration records and laboratory reference ranges for all local laboratories used for this study. The Sponsor will verify all equipment requirements at the study qualification and/or initiation. Sites with outdated and/or non-compliant equipment will either not be approved for study participation or will be advised to discontinue study-related activities should non-compliance be noted during regular study monitoring visits.
- All original informed consent forms with required signatures.
- All Ethics correspondence (i.e., informed consent [including any approved revisions], protocol, AEs, advertisements, newsletters).
- Copy of the Study Monitoring Log Sheet.
- Clinical and non-clinical supply shipment forms and device accountability logs.
- Copies of all correspondence pertaining to the study between Sponsor and the site.
- Copies of all SAEs reports submitted to the Sponsor.
- Copies of all Health Canada progress reports submitted to the site by the Sponsor.
- Site Delegation Signature Log.

10.2.5 Archiving

All study-related records must be maintained for at least 2 years after a marketing application (PMA) is approved for the study device; or if the application is not approved, until at least 2 years after shipment and delivery of the last device for investigational use is discontinued and FDA/health authorities or regulatory agencies have been notified of study closure. The Sponsor will notify the principal Investigator when records are no longer needed. The Investigator will not discard any records without notifying the Sponsor. If the Principal Investigator moves from the current investigational site, the Sponsor should be notified of the name of the person who will assume responsibility for maintenance of the records at the investigational site or the new address at which the records will be stored. The Investigator will notify the Sponsor as soon as possible in the event of accidental loss or destruction of any study documentation.

10.3 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.

10.4 Quality control

10.4.1 Monitoring

The Sponsor will ensure that the monitor will be appropriately trained and informed about the nature of the investigation. 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 subjects, 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.

10.4.2 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.

10.4.3 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.

10.5 Clinical Investigation Plan

10.5.1 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.

10.5.2 Deviations from Clinical Investigation Plan

A deviation refers to a study-related activity that is not in compliance with the investigational protocol. 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 analyzing them and assessing their significance. The appropriate ethics committee and institutional review board and regulatory authorities will be informed of any significant protocol deviations.

10.6 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.

10.7 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.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov.

10.8 Timetable

First subject first visit	Q3 2017
Last subject first visit	Q4 2017
Last subject last visit	Q4 2018

10.9 Definition of end of investigation

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

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11. ISO 8253-1 2010.

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12 APPENDICES

APPENDIX 1: NEW OSIA SPECIFIC INSTRUMENTS AND TEMPLATES

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

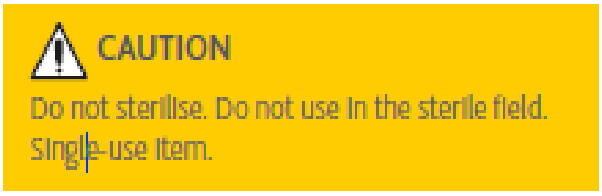
2. Clearance indicator. Used to ensure there is adequate clearance for the actuator above the level of bone. Reusable instrument.

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.



APPENDIX 2: OTHER DEVICES USED IN THE INVESTIGATION, NON-INVESTIGATIONAL

Product	**Article name**	**Sterile/ non-sterile**	**Single/ reusable**	**Regulatory approved**
	Surgical tools			
90469	Screwdriver Unigrip 95 mm	Non sterile	Reusable	Yes
92143	Multi wrench with ISO adapter	Non sterile	Reusable	Yes
90381	Machine Screwdriver Unigrip 25 mm	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 3 mm	Sterile	Single use	Yes
92141	Widening drill 4 mm	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			
N/A	Osia Fitting Software	NA	Reusable	No
N/A	Baha Fitting Software – CSDS (Download)	N/A	Reusable	Yes
P803254	Baha Fitting Software	NA	Reusable	Yes
B13033	BATTERY ZN AIR P675 IMPLANT PLUS	Non-sterile	Single use	Yes
Z60686	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
N/A	Osia Intraoperative Test Software CSDS	N/A	Reusable	No
	Cochlear SoftWear Pad	Non-sterile	Single use	Yes
P993402	Baha SoftWear Pad (15pcs)	Non-sterile	Single use	Yes