CLINICAL INVESTIGATION PLAN (CIP)

Implantation with the Nucleus® CI532 cochlear implant in Adults

Feasibility Study

Date: Version 3, April 2016

Sponsor	Cochlear Americas 13059 East Peakview Ave Centennial, CO 80111
Manufacturer	Cochlear Limited 1 University Avenue, Macquarie University, NSW 2109
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Clinical Research Organisation (or other institution involved)	Not applicable

Sponsor and Investigator Responsibilities

Investigation Title	Implantation with the Nucleus® CI532 cochlear implant in Adults.

Signature on behalf of Sponsor

I agree with the content in this clinical investigation plan, including all appendices.

Name	**Title**
Christine Menapace, M.A.	Vice President, Clinical, Quality, and Regulatory
Signature	**Date** (dd-mmm-yyyy)

Signature of Principal Investigator

I agree to the content of this clinical investigation plan, including all appendices.

Name	**Title**
J Thomas Roland Jr, MD	Principal Investigator
Signature	**Date** (dd-mmm-yyyy)

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1 CLINICAL INVESTIGATION SYNOPSIS

Investigation title	Implantation with the Nucleus® CI532 cochlear implant in Adults
Investigation number	CAM5631
Name of study device	Nucleus® CI532 cochlear implant
Investigators	J Thomas Roland, Jr. New York University
Investigation start	November 2015
Total expected duration of the clinical investigation	18 months
Enrolment period	3 months
Expected duration per subject	Up to 15 months/subject
Investigational design	Prospective, single-center, single arm with sequential enrollment.
Number of subjects	Up to 10 Adults

Inclusion criteria	1. Meet current cochlear implant indications at the implanting center. Current Nucleus cochlear implant indications include: a. Individuals 18 years of age or older who have bilateral, pre, peri or postlinguistic sensorineural hearing impairment b. Limited benefit from appropriate binaural hearing aids (verified by standard clinical practice), as defined by aided test scores of 50% correct or less in the ear to be implanted (60% or less in the best-aided listening condition) on tests of open set sentence recognition i. Consistent with the Minimum Speech Test Battery (2011), it is required that all subjects be evaluated at 60 dBA presentation level. c. Moderate to profound hearing loss in the low frequencies and profound (90 dB HL) hearing loss in the mid to high speech frequencies 2. In addition to meeting current cochlear implant indications, subjects must also possess preoperative unaided hearing thresholds between 40 and 65 dB HL, inclusively, at 250 & 500Hz in the ear to be implanted. a. Typical subjects will have the following audiometric configuration: i. Low frequency (250 – 500 Hz): Thresholds between 40 and 65 dB HL, inclusively ii. Mid to High frequency (above 1500 Hz): Thresholds greater than or equal to 90 dB HL 3. Fluent speaker in the local language used to assess clinical performance.

Exclusion criteria	1. Evidence of hearing loss prior to 5 years of age. 2. Sensorineural severe-to-profound hearing loss greater than 20 years at ≥ 2 kHz and above. 3. Simultaneous bilateral cochlear implantation or prior cochlear implantation in the ear to be implanted. 4. Medical or psychological conditions that contraindicate undergoing general anaesthesia or surgery. 5. Ossification, malformation or any other cochlear anomaly, such as common cavity, that might prevent complete insertion of the electrode array, as confirmed by medical examination. 6. Hearing impairment due to lesion or neuropathy of the acoustic nerve, VIII nerve or central auditory pathway. 7. Active middle-ear infection. 8. Tympanic membrane perforation. 9. Unrealistic expectations on the part of the subject, regarding the possible benefits, risks, and limitations that are inherent to the surgical procedure(s) and prosthetic devices. 10. Unwillingness or inability of the candidate to comply with all investigational requirements. 11. Patients with existing CSF shunts or drains, existing perilymph fistula, skull fracture or CSF leak. 12. Patients with recurrent episodes of bacterial meningitis.
Primary objectives	To obtain additional safety and efficacy data associated with CI532 cochlear implantation and postoperative fitting of the acoustic component in adults.
Secondary objectives	Patient reported outcome measures i) SSQ preoperatively and 6 months post-activation ii) GBI at 6 months post-activation
Primary endpoints	1. To evaluate preoperative to 6 months post-activation performance outcomes in the best unilateral listening condition using AzBio Sentences in noise. 2. Report of medical/surgical and device related adverse events compared to the current approved labelling with regard to type, frequency and seriousness at 6 months post-activation.
Secondary endpoints	1. To evaluate Patient Reported Outcomes (PRO) preoperatively to 6 months post-activation for the Speech Spatial and Quality of Hearing scale (SSQ) and the Glasgow Benefit Inventory (GBI) at 6 months post-activation.

2 OBJECTIVES AND HYPOTHESES

2.1 Objectives

The primary objective for the clinical investigation is to obtain additional safety and efficacy data associated with CI532 cochlear implantation in individuals who meet current indications for cochlear implantation but also have pre-operative hearing thresholds between 40 and 65 dB HL at 250 and 500 Hz in the ear to be implanted.

2.2 Hypotheses

As this is a feasibility study, there is no formal hypothesis to be accepted or rejected on the basis of statistical analysis in the current clinical investigation. Individual outcomes will be compared, along with group effects, across pre- and postoperative test conditions for the speech perception outcomes. Adverse events will be summarized by event type, severity, seriousness, as well as relatedness to the device and implant procedure will be reported and tabulated.

3 IDENTIFICATION AND DESCRIPTION OF THE STUDY DEVICE

Peri-modiolar electrodes such as the Contour Advance™ (CA) are designed to bring electrode contacts closer to the medial wall of the cochlea and so therefore closer to the spiral ganglion. Up until now these “pre-curved” electrodes have required a flexible metallic “stylet” to hold the electrode straight at the point of first introduction into the cochlea to avoid premature curling of the electrode. It is recommended that the electrode is advanced off the stylet™ (AOS) so that it follows the trajectory of the basal turn of the cochlea due to its curved shape. In this way contact with the lateral wall, which may produce trauma, may be avoided. Necessarily the cross-sectional area of the CA is somewhat larger than what may be required for a non-stylet “straight” array and there is always some chance that the stiffer array-stylet combination could still result in trauma such that the electrode array could dislocate between scala tympani and scala-media or scala-vestibuli, thus producing trauma to the interstitial membranes. In addition an electrode array in scala vestibuli is at a greater distance from the stimulation target (spiral ganglion cells) compared to one in scala tympani – thus current paths to these cells may be irregular and stimulation will be less selective, potentially reducing performance (1).

The device under investigation is the Nucleus® CI532 cochlear implant (Figure 1, left) which consists of a CI500 Series receiver/stimulator and a pre-curved, perimodiolar electrode array (EA32), which does not incorporate a lumen and stylet. Instead it has a thin electrode carrier which is introduced into the cochlea through a straightening sheath (Figure 1, right). The CI532 cochlear implant is manufactured by Cochlear Ltd, Macquarie University, Australia. Cochlear has been manufacturing cochlear implants for over 30 years. The Nucleus® CI532 cochlear implant was approved by the U.S. Food & Drug Administration for commercial use in March 2016.

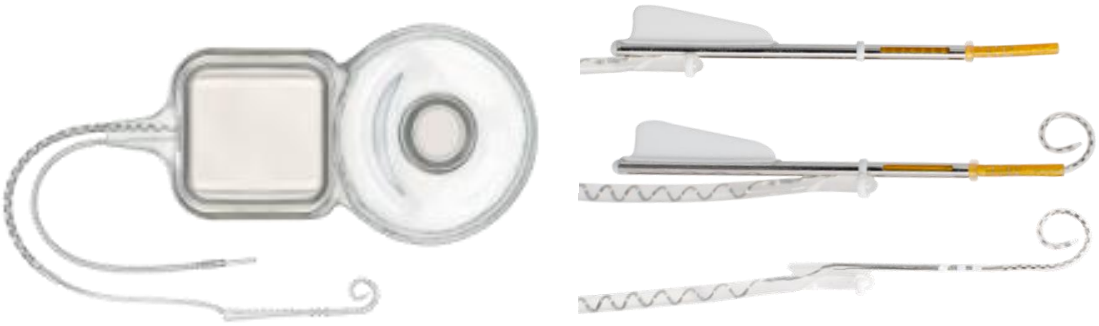

Figure 1: Left: The CI532 device (not to scale). Right: The EA32 electrode array loaded in the sheath (upper), advanced through the sheath, and with the sheath removed as in final situation (lower).

As for the CA, the EA32 array must be orientated correctly so that its curvature is in the plane of the basal turn, with electrodes towards the modiolus, and the sheath must be immobile during this process. The cross-sectional area of the EA32 is approximately 40% of that of the CA and thus it is overall less stiff than the CA; these two factors may allow the EA32 array to take up a position within scala tympani closer to the modiolus. The sheath is removed and discarded once the electrode is fully inserted.

The CI532 cochlear implant is a single use device intended for long term implantation under the skin in the mastoid region of either side of the head. Cochlear implantation can only be undertaken by an experienced surgical team, or under supervision of such a team.

The CI532 cochlear implant will be used in the current clinical investigation in adults who meet current indications for cochlear implantation in Australia and America. As the clinical investigation aims to assess the degree of hearing preservation with the CI532 device, candidates who are at the upper range of pre-operative residual hearing (40-65 dB HL at 500 Hz) will be recruited to participate.

The surgical approach will be cochlear implantation via posterior tympanotomy as described in the The Nucleus® CI532 cochlear implant with Slim Modiolar electrode Physician's Guide (2) on page 34. The bed for the CI500-series receiver-stimulator will be prepared before opening the cochlea, along with placement of the receiver-stimulator and extra-cochlea electrode. Since the CI532 implant electrode is compatible with both of the round window and cochleostomy approaches, the appearance of the RW and niche will be need to be visualized in order determine the choice of surgical approach (see page 64 in the Physician's Guide).

To utilize a round window approach:

1. Visualize the stapes to confirm the site of the round window, and visualize the round window membrane.
2. Remove the false membrane.

Please note: Do not open the round window membrane until immediately before insertion of the electrode.

To utilize a cochleostomy approach:

1. Visualize the stapes to confirm the site of the round window, and visualize the round window membrane.
2. Perform a cochleostomy into the scala tympani using a diamond burr at low speed. Position the cochleostomy inferior and slightly anterior to the round window membrane. It should be close to, or incorporating, the round window niche (RWN). A slight blue line of endosteum should become visible as the bone is being thinned for the cochleostomy. This indicates the location of the scala tympani.
3. Drill sufficient bone to expose at least 0.8–1.0 mm of endosteum.

Please note: To avoid risk of contamination, do not open the endosteum until immediately before insertion of the electrode.

4. Remove the final layer of bone.

Insertion of the array will be achieved using the advance-through-the-sheath technique described in the detailed step by step with imagery in the Physician's guide on pages 71-78.

Please note: the recommended cochlea opening is between 0.8 mm and 1.0 mm wide. With each CI532 an additional sterile silicon dummy implant and cochleostomy sizing tool is provided. The dummy implant allows checking of the size of the drilled-out implant bed. The sizing tool allows verification of the size of the cochleostomy hole such that the guide tube (yellow/orange figure 1 right) may easily enter the cochleostomy hole but that the stopper cannot (2). If the opening is larger than 1.4 mm, use the forceps holding the sheath handle to stabilize the sheath and ensure the stopper stays at the round window or cochleostomy opening.This ensures that intra-cochlear trauma is minimized and offers the potential for hearing preservation in as many cases as possible.

The EA32 electrode (Figure 1, right) is placed into the cochlea and carries twenty-two electrode contacts. In addition there are two extra-cochlear return electrode contacts; one is connected to the CI500 body via a lead wire and placed under the temporalis muscle and the other is an exposed area of the case of the CI500 (Figure 1, left).

The CI532 is a device which is commercially available for implantation based on FDA approval in March 2016. Orders for devices will be placed in the Oracle system, with shipment to be approved by the Clinical Project Manager, Cochlear Americas. Devices are identified by unique serial numbers.

This device when combined with the approved external Nucleus 6 Sound Processor (SP) (CP900 Series) provides electrical stimulation to the auditory nerve which can be interpreted as sound by the hearing impaired recipient. Biphasic current pulses at the electrode contacts are generated by the CI500-series receiver/stimulator which is controlled by the external Sound Processor via a transcutaneous radio link.

Standard activation of the CI532 will be achieved using Custom Sound software running on a PC equipped with a Nucleus Pod programming interface. Electrically-evoked Compound Action Potentials (ECAPs) may be measured using either Custom Sound or Custom Sound EP software during surgery or at the device activation appointment.

The external envelope materials of the CI532, and sterile accessories, and the Nucleus 6 CP900 Sound Processors are biocompatible according to applicable standards (i.e. ISO 10993: 2009/AC:2010).

4 DESIGN OF THE CLINICAL INVESTIGATION

4.1 General

The Implantation of the Cochlear™ Nucleus® CI532 in Adults feasibility study will be conducted as a single-site, prospective, single-arm clinical study, evaluating the safety and functionality of the Cochlear Nucleus CI532 cochlear implant in up to 10 subjects who meet current cochlear implant indications with low frequency unaided thresholds at 250 and 500 Hz between 40 and 65 dB HL. A single-subject repeated-measures analysis will be employed whereby subjects will act as their own control. A single-subject research design is appropriate since it accommodates the heterogeneity that characterizes hearing-impaired populations. Blinding procedures are not appropriate for this trial design, as it is not possible to conceal the presence, or absence, of a cochlear implant from device recipients and/or clinical investigators.

4.2 Study device and comparator

Subjects will be implanted with the study device, the Nucleus CI532 cochlear implant. The device will be activated at approximately 1 month post-operatively according to the investigational site's standard clinical procedures. Activation generally consists of determination of active electrodes via impedance measurements followed by the determination of subjective threshold (T) and comfortable (C) levels of stimulation (current amplitude) for each electrode. The Nucleus CP900 Series Sound Processor, is programmed such that input sound frequencies are allocated across the electrode array with input sound intensities being converted to stimulation levels between Ts and Cs. According to the postoperative audiogram, a subject may also receive the acoustic component. The acoustic component will be determined and fit according to commercial clinical recommendations and training. T and C-levels as well as use of the acoustic component may be re-evaluated at intervals after activation to take into account acclimatization of the subject as well as postoperative residual hearing status.

This is a single-arm, single center investigation. The comparator device is one of the sponsor's other current commercially available pre-formed or peri-modiolar Contour Advance electrode which may be connected to the CI24RE "Freedom" receiver-stimulator electronics module or the later CI500 module. There is no difference in electronic capability between the CI24RE and CI500; the difference lies in the form factor. There is no proposed concurrent medical device or medication. The investigational site may use systemic application of corticosteroids and/or

antibiotics at time of surgery possibly followed by oral application according to clinical standard of care.

4.3 Endpoints

4.3.1 Primary endpoints

The six month post-activation visit serves as the primary endpoint for data collection related to:

1. Efficacy – To evaluate preoperative to 6 months post-activation performance outcomes in the best unilateral listening condition using AzBio Sentences in speech weighted noise (SWN).
2. Safety – Report of medical/surgical and device related adverse events compared to the current approved labelling with regard to type, frequency and seriousness at 6 months post-activation.

4.3.2 Secondary endpoints

To evaluate Patient Reported Outcomes (PRO) preoperatively to 6 months post-activation for the Speech Spatial and Quality of Hearing scale (SSQ) and the Glasgow Benefit Inventory (GBI) at 6 months post-activation.

4.3.2.1 Speech, Spatial and Qualities of Hearing scale (SSQ)

The six month post-activation visit serves as the secondary endpoint for data collection related to self-reported auditory disability and quality assessment with the SSQ for the CI532 cochlear implant.

4.3.2.2 Glasgow Benefit Inventory

The six month post-activation visit serves as the secondary endpoint related to health utility data collection with the GBI for the CI532 cochlear implant.

4.4 Additional clinical measures

4.4.1 Audiometric assessment

Unaided audiometric thresholds obtained for each ear[1], with insert earphones, using the standard audiometric technique for pure-tone air and bone conduction testing. Aided thresholds will be obtained for each ear.

4.4.2 Speech perception

For individuals who utilize the acoustic component, the electric alone condition will also be assessed. Subjects will also be assessed using the CNC monosyllabic word test in quiet in the best unilateral listening condition.

[1] As these subjects may have measureable low-frequency hearing, it is important that appropriate consideration be made for masking or plugging the contralateral ear during unilateral testing in the sound field.

4.4.3 Electrode placement

An X-ray will be obtained intraoperatively (preferably a lateral or modified Stenver's view) to confirm proper electrode placement.

4.4.4 Device characteristics

Device characteristics such as impedance measurements, programming map parameters, psychophysical threshold and comfort levels, and neural response telemetry (NRT) will be exported into an anonymous .cdx file.

4.5 Equipment

Speech perception performance in quiet will be assessed using a loud speaker configuration with the signal from the front (S0). Speech perception performance in noise will be assessed using a loud speaker configuration with signal from the front and noise from the implanted side (S0N90 or S0N270) as shown in Figure 2.

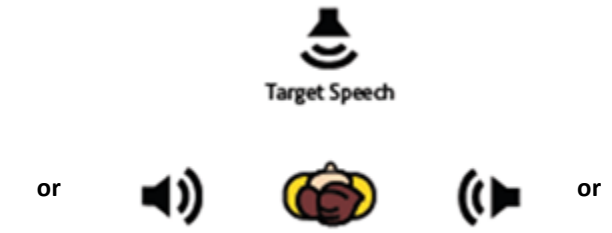

Figure 2: Speaker orientation for speech perception assessment

The loudspeakers are located at head height for a seated subject (reference point). The distance from the loudspeaker from the reference point is approximately one meter. There will be defined locations for the loudspeakers and subject within the test environment. Sound field calibration of the Average Sound Level (Leq) is performed prior to each visit using a sound level meter (SLM) using a dB A-weighting (dBA), slow time weighting.

4.6 Investigation schedule

Table 1: Investigation schedule

Procedure	Pre-op	Surgery	Activation	3 months post-activation	6 months post-activation	12 months post-activation
Medical history	x					
X-ray		x				
Impedances			x	x	x	x
T/C Levels			x	x	x	x
Speech Perception Testing	x			x	x	x
Unaided Audiogram	x		x	x	x	x
SSQ	x				x	
GBI					x	
Surgical Questionnaire		x				
Adverse Events		x	x	x	x	x

4.7 Subjects

4.7.1 Inclusion Criteria

1. Meet current cochlear implant indications at the implanting center. Current Nucleus cochlear implant indications include:
    a. Individuals 18 years of age or older who have bilateral, pre, peri or postlinguistic sensorineural hearing impairment
    b. Limited benefit from appropriate binaural hearing aids (verified by standard clinical practice), as defined by aided test scores of 50% correct or less in the ear to be implanted (60% or less in the best-aided listening condition) on tests of open set sentence recognition
        i. Consistent with the Minimum Speech Test Battery (2011), it is required that all subjects be evaluated at 60 dBA presentation level.
    c. Moderate to profound hearing loss in the low frequencies and profound (90 dB HL) hearing loss in the mid to high speech frequencies

2. In addition to meeting current cochlear implant indications, subjects must also possess preoperative unaided hearing thresholds between 40 and 65 dB HL at 250 & 500Hz in the ear to be implanted[2]
    a. Typical subjects will have the following audiometric configuration:
        i. Low frequency (250 – 500 Hz): Thresholds between 40 and 65 dB HL, inclusively
        ii. Mid to High frequency (above 1500 Hz): Thresholds greater than or equal to 90 dB HL
3. Fluent speaker in the local language used to assess clinical performance[3]

4.7.2 Exclusion Criteria

1. Evidence of hearing loss prior to 5 years of age
2. Sensorineural severe-to-profound hearing loss greater than 20 years at ≥ 2 kHz and above
3. Simultaneous bilateral cochlear implantation or prior cochlear implantation in the ear to be implanted
4. Medical or psychological conditions that contraindicate undergoing general anaesthesia or surgery
5. Ossification, malformation or any other cochlear anomaly, such as common cavity, that might prevent complete insertion of the electrode array, as confirmed by medical examination
6. Hearing impairment due to lesion or neuropathy of the acoustic nerve, VIII nerve or central auditory pathway
7. Active middle-ear infection
8. Tympanic membrane perforation
9. Unrealistic expectations on the part of the subject, regarding the possible benefits, risks, and limitations that are inherent to the surgical procedure(s) and prosthetic devices as determined by the Investigator
10. Unwillingness or inability of the candidate to comply with all investigational requirements as determined by the Investigator
11. Patients with existing CSF shunts or drains, existing perilymph fistula, skull fracture or CSF leak
12. Patients with recurrent episodes of bacterial meningitis

[2] If it is more than 90 days past the date of the Candidacy Evaluation, candidacy needs to be reconfirmed by repeating hearing threshold test measures at 250 and 500Hz. Any changes observed will need to be reviewed in consultation with the Sponsor prior to surgery occurring. If candidate is not currently aided in the ear to be implanted, documentation of previous hearing aid trial is required.

[3] As judged by the investigator i.e. able to complete the speech perception assessments tasks and questionnaires.

4.7.3 Number of subjects required

The proposed study is designed to collect safety and efficacy data associated with CI532 cochlear implantation and the feasibility of fitting of the acoustic component postoperatively in adults. The protocol describes a feasibility study within a single site and a limited number of subjects (up to 10 subjects). Based on the data collected in IDE G120234, assuming the observed mean and standard deviation for each endpoint are representative of the corresponding values for the population, it was determined that a minimum of 23 evaluable subjects would provide at least 90% power for a hypothesis test of superiority at the one-sided 0.025 alpha level. Allowance of 10% to account for possible attrition brings the sample size to 25 subjects to be recruited into the study and implanted. The planned sample size of up to 10 subjects will not provide adequate power for the primary efficacy endpoints hence the proposal for a feasibility study design.

The following general assumptions have been made:

- Paired t-tests
- One-sided 0.025 or 0.05 alpha levels
- Assumed distribution for population (mean, SD) based on IDE G120234
- Desire for 80% or 90% power

Power for the primary test metric AzBio Sentences in SWN under a variety of assumptions is provided below.

Scenario	Minimum Evaluable Sample Size
One-sided 0.025 alpha, 80% power	18
One-sided 0.025 alpha, 90% power	23
One-sided 0.05 alpha, 80% power	16
One-sided 0.05 alpha, 90% power	20

Subject enrollment is estimated to take three months to recruit up to 10 subjects at a single investigational site. The enrollment period may be extended if required.

4.7.4 Criteria and procedures for subject's withdrawal or discontinuation

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[4]
- Investigator decision[5]
- 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, IRB and FDA.

During surgery, an alternative device (e.g., CI522 or CI512) may be implanted in subjects where there are substantial difficulties with the CI532. These subjects will continue the clinical investigation and their outcomes will be compared to those subjects who received the CI532 device.

4.7.5 Subject replacement

The total number of subjects proposed for this clinical investigation is up to 10. If a subject withdraws pre-operatively, they will be replaced by a newly recruited subject who meets the selection criteria for participation.

4.7.6 Point of enrollment

Subjects are recruited to the study by the investigators usually during the course of medical consultation. Subjects will be sequentially enrolled once Cochlear Americas receives a properly executed Informed Consent form and has approved the preoperative candidacy evaluation.

4.7.7 Total expected duration of the clinical investigation

The total expected duration of the clinical investigation is 18 months. The total duration will be dependent on the ability to recruit the required number of subjects within the enrollment period.

5 JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION

A multi-center clinical early feasibility trial was performed with 17 cases being implanted with version 1 of the electrode array/sheath assembly (3). Electrode tip fold-over was identified in 32% of cases and due to this complication, 23% of cases received a commercial back-up device (CI24RE(CA) or CI512). Complications were related to device deficiencies and surgical protocol deviations. Hearing preservation was generally poor and most subjects lost their residual

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

[5] 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.

hearing in the implanted ear. The participants recruited for the early feasibility trial met current local indications for a conventional implant. The inclusion criteria specified an unaided hearing threshold in the ear to be implanted of equal to or better than 80 dB HL at 500Hz. Speech perception in quiet and noise significantly improved pre-operatively-to-post-operatively. Follow-up of these cases is now more than 5 years with no device related adverse events reported – all devices remain functional and in place.

Rotation of the electrode in the sheath may have contributed to the adverse device effects seen in the early feasibility trial and lead to further sheath design by Cochlear Limited. Most of the development focussed on the sheath until version 4 where the sheath to guide-tube assembly was reconfigured to further improve handling and visibility. In the intermediate designs tip folding occurrence was reduced by removing rotation and finally by modification of the slit in the sheath. The slit allows the sheath to be removed after the electrode is fully deployed. The final version improved the stability of the sheath especially when some bending of the array and sheath occurs.

Pre-clinical testing with the CI532 was performed with four versions of the electrode-sheath assembly over four rounds of formal temporal bone trials. The temporal bone data on the EA32 (using the latest sheath design) shows perimodiolar positioning in a large majority of cases with a relatively low potential for intra-cochlear trauma shown by a dislocation rate of 3.3%. Once use errors were taken into account the tip fold-over rate was 3/110 or <3%.

Currently, an outside the United States (OUS) multicenter clinical investigation is being undertaken to determine if a low rate of dislocation can be achieved in clinical cases. Fourteen adult candidates have been successfully implanted with the CI532 device (Melbourne, Australia and Las Palmas, Spain) at the time of this submission with no scala dislocation or electrode tip fold-over. Due to early success in the positioning of the CI532 device, further clinical evaluation is warranted to assess the feasibility of accessing acoustic hearing postoperatively in a clinical population with greater potential to preserve residual hearing.

The primary objectives of the clinical investigation is to 1) evaluate preoperative to 6 months post-activation performance outcomes in the best unilateral listening condition using AzBio Sentences in speech-weighted noise (SWN) and 2) report the medical/surgical and device related adverse events compared to the current approved labelling with regard to type, frequency and seriousness at 6 months post-activation. In order to demonstrate the atraumatic nature of the CI532 electrode design and insertion technique, as well as the possibility of fitting of the acoustic component postoperatively, the inclusion criteria has been structured to capture subjects who currently meet the clinical criteria for cochlear implantation but who also possess unaided audiometric thresholds between 40 and 65 dB HL in the low frequencies. The secondary objectives of this clinical investigation are to evaluate Patient Reported Outcomes (PRO) preoperatively to 6 months postactivation for the Speech Spatial and Quality of Hearing scale (SSQ) and the Glasgow Benefit Inventory (GBI) at 6 months postactivation. The outcomes from this feasibility study may be used to support the development of a randomized multicenter

clinical investigation evaluating the functional hearing preservation with the CI532 cochlear implant.

6 CLAIMS AND INTENDED PERFORMANCE

The claims and intended performance of the study device that are to be verified are:

1. The number and percentage of subjects who were able to be fit with the acoustic component postoperatively.
2. Pre-to-post performance benefits with the CI532 cochlear implant for speech recognition in the best unilateral listening condition.

7 PROCEDURES

7.1 Medical history and Counseling

Information regarding subject hearing-history (e.g., etiology, onset of hearing loss, duration of severe-to-profound hearing loss, amplification use) will be obtained and reported on the respective case-report form. In addition, patients will be carefully and extensively counseled to ensure that their expectations from cochlear implantation are reasonable and appropriate (as determined by the Investigator).

7.2 Audiogram (Candidacy, Activation, 3, 6 and 12 months post-activation)

An unaided audiogram will be performed for both ears at Candidacy[6], Initial Activation, 3, 6 and 12 months post-activation at the following pure-tone frequencies:

- Air Conduction: 125, 250, 500, 750, 1000, 2000, 3000, 4000, 6000 & 8000 Hz

Air conduction thresholds >80 dB HL at 125 Hz, >90 dB HL at 250 Hz, >100 dB at 80000Hz and >120 dB for other test frequencies will be marked NR (no response). Thresholds that exceed the air conduction limits of the audiometer, where the recipient reports feeling the acoustic stimuli, shall be recorded as vibrotactile (VT).

- Bone conduction: 125[7], 250, 500, 750, 1000, 2000, 3000, 4000 Hz

Bone conduction thresholds >20 dB HL at 125 Hz, >30 dB HL at 250 Hz, >60 dB HL at 500 Hz and >70 dB HL for other test frequencies will be marked NR (no response).

[6] If it is more than 90 days past the date of the Candidacy Evaluation, candidacy needs to be reconfirmed by repeating audiometric threshold test measures. Any changes observed will need to be reviewed in consultation with the Sponsor prior to surgery occurring.

[7] Bone conduction measures at 125 Hz are optional based on potential audiometric equipment limitations.

An aided audiogram will be performed for both ears at candidacy, and the implanted ear at initial activation[8], three, six and 12 months post-activation at the following frequencies using warble tones:

- Aided thresholds: 125, 250, 500, 750, 1000, 2000, 3000, 4000 Hz

7.3 Speech recognition (Candidacy, 3, 6 and 12 months post-activation)

Speech recognition will be measured pre-operatively, and at 3, 6, and 12 months post activation. Pre-operatively, speech recognition will be evaluated in the unilateral aided condition with the contralateral ear masked or plugged. Post-activation, the best unilateral listening condition will be evaluated; "Implant ear" using the acoustic component and/or the CI SP alone on one ear with the contra-lateral ear plugged or masked. If the subject uses the acoustic component, speech perception will also be completed as electric alone. Post-activation speech recognition will be evaluated with default input processing options.

Assessment of speech perception in quiet will be measured using two lists of CNC monosyllabic word test (7) at 60 dBA in the S0 speaker orientation (Figure 2).

Assessment of speech understanding in noise will be measured using a list of 20 sentences drawn from the AzBio sentences lists (8) at 60 dBA at a fixed +5 dB signal-to-noise ratio (SNR) in the S0N90 or S0N270 speaker orientation (Figure 2). The competing noise will be speech weighted noise (SWN).

Test lists will be randomized throughout the clinical investigation in order to avoid learning effects.

Performance benefits are change in scores pre- to post-operatively:

1. Gain in speech recognition in quiet (% correct)
2. Gain in speech recognition in noise (% correct)

7.4 Speech, Spatial, Qualities of Hearing Scale – SSQ (Candidacy & 6 months post-activation)

Subjective quality assessment will be measured using the SSQ preoperatively and again at 6 months post-activation.

Performance benefits are a change in scores pre- to post-operatively:

1. Gain in SSQ score (-10 to +10)

[8] Assessing aided thresholds after the initial activation will only be conducted if there is a shift in unaided hearing of more than 10 dB HL (for the better or worse) at two or more aidable frequencies.

7.5 Glasgow Benefit Inventory – GBI (6 months post-activation)

Health Utility assessment will measured using the GBI at six months post-operatively.

Performance benefits are a change in scores pre- to post-operatively:

1. GBI score (-100 to +100)

7.6 Surgical Questionnaire – Intraoperatively

Surgical questionnaire will be completed by the implanting surgeon for each subject implanted.

7.7 Video (Surgery)

Surgery may be recorded via a video camera connected to the surgeon's microscope.

7.8 Imaging: X-ray (Surgery)

The presence of tip fold-over may be detected intra-operatively via planar X-ray, so that it may be corrected in-situ. Consistent with the Nucleus® CI532 cochlear implant with Slim Modiolar electrode Physician's Guide on page 81, an X-ray will be obtained prior to closure (preferably a lateral or modified Stenvers view) to confirm proper electrode placement.

7.9 Activation (approximately 1 month post-surgery)

The CI532 cochlear implant will be activated with a commercially available Nucleus CP910 or CP920 Sound Processor and Custom Sound programming software. This will take place approximately 1 month after surgery (plus/minus 2 weeks).

Impedances and T/C levels will be collected during the visit. These data will be extracted from anonymized computer record files ("CDX") produced by the Custom Sound software.

Initially the default ACE sound coding strategy will be used with the parameters pulse rate 900 pps per channel, 25 µs / phase, mode MP1+2, and 8 maxima. These parameters may be adjusted afterward according to local procedures to improve subjective sound quality, if deemed necessary by the clinician. The sound processor should be loaded with the currently available, default input processing options.

7.10 Device characteristics (Activation and 6 months post-activation)

Device characteristics will be recorded at every post-activation visit and maintained within the subjects anonymous .cdx file.

7.11 Safety

The investigator will complete an Adverse Event (AE) and or Adverse Device Effect Case Report Form (AE and ADE CRF) if any AE or ADE is reported or observed for a subject during the investigation, even if they were acknowledged as risk factors in the Informed Consent Form.

7.12 Medical care post-investigation

Routine medical care from the implanting center will be provided for the subjects during, as well as, after the clinical investigation has been completed. Subjects will be followed-up as per the centers standard clinical procedures.

7.13 Monitoring Plan

The sponsor will appoint appropriately trained monitors to review the progress of the study and assure the quality and integrity of data accumulated. Clinical monitors, as representatives of the Sponsor, have the obligation to provide site qualification and initiation visits as well as regular site visits. The study monitors will be employees of the sponsor, Cochlear Americas, or any contracted vendors qualified by experience and training to conduct study site monitoring for this investigation.

Study monitors, employed by Cochlear Americas, for this study will be:

Ginger Grant, AuD 13059 E Peakview Avenue Centennial, Colorado 80111	Kimberly Nix, AuD 13059 E Peakview Avenue Centennial, Colorado 80111
Lori O'Neill, AuD 13059 E Peakview Avenue Centennial, Colorado 80111	Megan Mears, AuD 13059 E Peakview Avenue Centennial, Colorado 80111
Samantha Albawab, CRA 13059 E Peakview Avenue Centennial, Colorado 80111	Shanell Laner 13059 E Peakview Avenue Centennial, Colorado 80111

All data generated during this study and the source documents from which they originated are open to inspection by the Sponsor or its representative, the FDA, and other regulatory agencies. The Study Monitor will ensure study conduct is within compliance with regional requirements and ISO14155, where applicable.

Source documents are defined as any printed, optical or electronic document containing source data (hospital records, audiograms, speech test results, laboratory notes, device accountability records, radiographs, records kept at the investigational site) containing data necessary for the reconstruction and evaluation of the clinical investigation. The extent of source data verification is defined in the Monitoring Plan. The investigator shall provide all requested documentation in a timely and organized manner.

The investigator has to inform the Sponsor about any additional local requirements that may impact the work of a monitor especially if access to source data may be limited by local regulations. This is to ensure any necessary action to be taken before the study start to allow proper monitoring according to regional requirements and the ISO Guidance, where applicable.

The Study Monitor shall inform the Sponsor about any problems relating to facilities, technical equipment or medical staff at the study site. The Study Monitor shall provide the CPM with written reports, after each visit or contact with the investigational site.

Upon completion of the study, the clinical monitor will conduct a study close-out of the investigational site. The objectives of this visit are to ascertain that all subjects are accounted for, that the regulatory records and reports are complete, verify that study device and other supplies have been accounted for and ensure that the Investigator is aware of his/her responsibilities post-study.

8 REPORTING PROCESS FOR ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES

8.1 Definitions

All definitions are according to the EN ISO 14155:2011 standard.

8.1.1 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 investigational medical device.

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.

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

8.1.2 Adverse device effect (ADE)

Adverse device effect is an adverse event related to the use of an investigational medical device.

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

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

8.1.3 Device deficiency (DD)

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

NOTE Device deficiencies include malfunctions, use errors, and inadequate labelling.

8.1.4 Serious adverse event (SAE)

A serious adverse event is any adverse event that:

1) led to a death,
2) led to a serious deterioration in the health of the subject that either resulted in
   a) a life-threatening illness or injury, or
   b) a permanent impairment of a body structure or a body function, or
   c) in-patient hospitalization or prolonged hospitalization, or
   d) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
3) 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.

8.1.5 Unanticipated adverse device effect (UADE)

An unanticipated serious adverse device effect is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the risk analysis report (for the investigational device or its comparator).

8.2 Reporting process for adverse events

8.2.1 Unanticipated Adverse Device Effects

Unanticipated adverse device effects (UADEs) must be reported directly to the clinical center's reviewing IRB and the Sponsor, Cochlear Americas, within 10 working days of knowledge of the event, or as dictated by the specific IRB policy, whichever is sooner. Information regarding the UADE will be recorded on the *Unanticipated Adverse Device Effect Report,* provided with the CRFs for the study.

8.2.2 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 a *Follow Up to a Previously Reported Adverse Event Questionnaire,* provided with the CRFs for the study.

8.2.3 **Sponsor's Responsibilities**

All AE, DD and SAEs will be reported in the Annual Progress Report (APR) to FDA in accordance with the IDE regulation [FDA 21 CFR Part 812.150(b)(5)].

All unanticipated adverse device effects (UADEs) will be reported to FDA within 10 calendar days of the event in accordance with FDA 21 CFR Part 812.46(b) and 812.150(b)(1).

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.

8.3 Data Monitoring Committee

No DMC will be established.

9 STUDY COMPLETION

9.1 Completed Subjects

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

9.2 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[9]
- Investigator decision[10]

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

[10] 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.

- 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, IRB and FDA.

9.3 Premature Study Termination

The Sponsor reserves the right to discontinue the study for any safety, ethical or administrative reason at any time. Subjects already implanted with the device being studied will continue to be supported, independent of any decision made about study continuation.

10 STATISTICAL CONSIDERATIONS

All subjects who are recruited to the clinical investigation will constitute the intention-to-treat (ITT) population for the purposes of safety evaluation. Only subjects implanted with the CI532 and completed per the protocol will be considered as the completed cases (CC) population and per protocol (PP).

As this is a feasibility clinical investigation, there have been no formal power or sample size estimations performed for the primary objectives. The intent of the proposed investigation is to establish preliminary safety and effectiveness data. There are no pass/fail criteria to be applied to the results of the clinical investigation.

10.1 Efficacy Measurements

At a minimum, individual data will be tabulated and summarized for all measures to establish the proportions of those subjects showing improvement, no change, and decrement in performance.

The efficacy objectives include:

a) To understand if subjects implanted with the CI532 can retain low frequency thresholds and be fit with the acoustic component

Audiometric data will be collected and acoustic fittings will be tracked at each follow up time point. For those fit with the acoustic component, outcomes will be assessed with and without the acoustic component.

b) To understand if implantation with the CI532 results in improved postoperative speech perception outcomes in both quiet and noise when using the best unilateral listening condition

Device efficacy will be evaluated by comparisons of group and individual performance pre- and postoperatively at 3, 6, and 12-months post-activation. Performance benefits are change in scores pre- to post-operatively:

- Gain in speech recognition in quiet on CNC words (% correct)
- Gain in speech recognition in noise on AzBio Sentences (% correct)

c) To understand if implantation with the CI532 results in improved patient reported hearing performance and health utility

Scores from the SSQ obtained postoperatively will be compared with those obtained preoperatively, prior to implantation. The SSQ will act to provide a measure of hearing performance as perceived by the subjects. The GBI will provide a measure of change in health status as a result of cochlear implantation. Since the GBI is structured as a post-intervention (change) metric, there will be no preoperative measures derived for comparison with postoperative scores.

10.2 Safety Measurements

No formal statistical hypothesis will be tested. The number and percent of patients with adverse events will be reported and tabulated, including the number and percentage of tip fold overs. Adverse events will be summarized by event type, severity, seriousness, as well as relatedness to the device and implant procedure. Since the proposed study involves a limited number of subjects, group analyses are not planned.

10.3 Baseline Characteristics

The characteristics of the study group will be presented descriptively. Quantitative variables such as age will be presented with mean, standard deviation, median, minimum and maximum and 95% CI. Qualitative variables such as age or gender will be presented as percentages and observed frequencies. If differences in outcome are found for subgroups defined by baseline age or gender, analyses will be performed to explore the possible role of other baseline characteristics to explain the results.

10.4 Missing Data

All efforts will be put forth to ensure near complete follow-up, with particular focus on the assessment of the primary outcomes and occurrence of adverse events. A reminder of subject follow-up due date will be provided to participating centres to facilitate scheduling of the follow-up visit.

In the event a subject is withdrawn prior to the six month post-activation assessment, the analysis of the primary endpoint will involve imputing the last data point captured (candidacy, activation or 3 months post-activation) for the six month post-activation assessment. The p-value for the primary statistical hypothesis tests will be calculated using this imputation to understand the impact of missing data on the primary results.

11 RISKS AND BENEFITS OF THE STUDY DEVICE AND CLINICAL INVESTIGATION

For this clinical investigation, safety will be defined as freedom from device or procedure-related adverse events compared to the commercially available Cochlear Nucleus CI24RE. Additionally, the number and percentage of tip fold overs as confirmed by intraoperative x-ray will be reported.

11.1 Anticipated clinical benefits

Analysis of the final positions of EA32 electrode in temporal bones, as reported above in Section 5, revealed a low incidence of intra-cochlear trauma shown by a dislocation rate of 3.3%. The absence of dislocation is correlated with higher speech recognition scores (1, 4). In addition, close proximity of the electrode array to the medial wall is correlated with higher speech recognition scores (1). In both temporal bones and in the previous early feasibility study, the thinness of the pre-formed EA32 array gave in most cases wrapping factors of ~0.5 as estimated from images of temporal bones – this is at the best-performing end of the distribution presented by Holden et al. (1) Therefore due to low potential for trauma and close proximity of electrode contacts to the modiolus, we expect a high clinical benefit for patients from the CI532.

11.2 Anticipated adverse device effects

Subjects are exposed to the anticipated adverse device, and or procedure related effects associated with standard cochlear implant surgery and general anaesthesia.

Adverse effects associated with any cochlear implant are:

- Individuals are exposed to the normal risks associated with surgery and general anaesthesia.

- The surgical procedure may result in infection or bleeding, numbness or stiffness about the ear, injury to or stimulation of the facial nerve, taste disturbance, dizziness, increased tinnitus, neck pain, or perilymph fluid leak. Inner ear fluid leak may result in meningitis.

- The cochlear implant results in a palpable lump under the skin just behind the ear. The presence of a foreign body under the skin may cause irritation, inflammation or breakdown of the skin and, in some cases, extrusion of the device. The electrode array may migrate partially or completely out of the cochlea, resulting in decreased hearing ability. The electrode lead may perforate structures of the external ear, such as the tympanic membrane or canal wall. Misplacement of the electrode array may result in the perception of non-auditory sensations. Such complications may require additional medical treatment, surgery and/or removal of the device.

- Electrical stimulation may result in increased tinnitus, facial nerve stimulation, dizziness or pain.

- Individuals who have residual hearing in the ear selected for the cochlear implant have a slightly greater risk of short-term postoperative dizziness than individuals with no residual hearing in that ear.

- The long term effects of electrode insertion trauma or from chronic electrical stimulation are unknown. Such effects may include new bone growth in the cochlea or deterioration of the nerve cells. These effects may preclude replacement of the electrode array or may lead to eventual deterioration of cochlear response.

- Failure of component parts (both external and internal) could result in the perception of an uncomfortably loud sound sensation or no sound. Failure of various component parts of the implanted device could require removal or replacement of the implant, or a reduction in the number of electrodes used.

- Inserting the electrode into the cochlea may result in a partial or complete loss of residual hearing in the implanted ear.

Residual risks for the study device compared to a similar device, such as the Nucleus CI512, relate to use errors which may increase the risk of tip fold-over. It should be noted that tip folding is not unknown in similar pre-curved arrays or in straight arrays. The presence of a tip fold-over does not usually produce any untoward clinical symptoms however; it is likely that the distribution of current produced by the electrode array would be perturbed such that performance outcomes could be limited.

All residual risks for the device will be described within the Informed Consent.

11.3 Risks associated with participation in the clinical investigation

There are no anticipated adverse reactions specific to the study device other than those usually associated with cochlear implantation (as listed above) and concomitant medical treatments (2).

11.4 Risk mitigation

Tip fold-over of the array may necessitate re-implantation. Tip fold-over is typically detected via imaging. In this case, the EA32 electrode may be removed from the cochlea, re-loaded and re-inserted or alternatively, the CI532 device may be explanted and replaced with the back-up device.

More detail on device specific risks and how they are mitigated may be found in the Physician's Guide (2). All surgeons will receive surgical training in the use and handling of the CI532 cochlear implant as part of study initiation. In addition, Cochlear surgical support may be present during surgeries performed by the investigational site.

11.5 Risk-to-benefit rationale

The improved likelihood of correct scala tympani placement, increased proximity to the modiolus, and reduced potential for trauma for the CI532 may provide better access to residual

hearing postoperatively for patients with moderate levels of preoperative hearing compared to the existing CI512 or CI24RE(CA) implants equipped with CA electrode arrays.

In conclusion, the risk benefit ratio of participating in this study is similar to the risk benefit ratio of receiving treatment with a commercially approved Nucleus cochlear implant.

12 GOOD CLINICAL PRACTICE

12.1 Declaration of Helsinki and compliance with standards

The clinical investigation shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (2013), the ISO 14155:2011 Standard and any regional or national regulations, as appropriate.

12.2 Institutional Review Board (IRB)

Prior to the initiation of the study, the Protocol, the Informed Consent Form, and other supporting documentation must be submitted to the Institutional Review Board (IRB) for approval after FDA conditional or final approval. A copy of the IRB approval letter for the Protocol, the Informed Consent, and the Protocol Signature page must be submitted to the Sponsor prior to the consent of the first subject. The study site must maintain an accurate and complete record of all reports, documents, and other submissions made to the IRB concerning this protocol.

A list of the IRB members, their titles or occupations, and their institutional affiliation, or an IRB assurance number and their contact information must be provided to the Sponsor or its designee prior to release of study supplies. Additionally, the Chair of the IRB must be identified.

FDA/relevant health authority regulations require that all advertisements for subject recruitment be approved by an IRB prior to implementation. The complete text and format must be submitted to the Sponsor or its designee for approval prior to IRB submission.

13 QUALITY CONTROL AND ASSURANCE

Sponsor employees and/or their contracted representatives utilize Standard Operating Procedures (SOP) designed to ensure that clinical study procedures and documentation are consistently conducted/prepared to the highest quality standards. Safety data adjudication will be conducted by the Sponsor's Chief Medical Officer, in accordance with these SOPs. These SOPs require compliance with federal regulations and Good Clinical Practice guidance.

14 INFORMED CONSENT PROCESS

A sample informed consent form containing the required elements of informed consent is provided by the Sponsor once FDA approved. Any changes made to this sample must be

approved by the Sponsor, or its designee, prior to submission to an IRB. After approval by the Sponsor, the informed consent must be submitted to and approved by an IRB.

14.1 Obtaining informed consent

It is the responsibility of the investigator to inform each subject prior to the initial study evaluation, of the purpose of this clinical trial, including possible risks and benefits, and document the informed consent process in the subject's chart. The investigator shall obtain written informed consent using an approved Informed Consent Form from the subject prior to any clinical investigation related examination or activity. Ample time shall be provided for the subject to inquire about details of the clinical investigation and to decide whether to participate. All questions about the clinical investigation shall be answered to the satisfaction of the subject or the subject's legally acceptable representative. Subjects shall not be coerced or unduly influenced to participate or to continue to participate in a clinical investigation.

Each subject and the person who conducted the informed consent discussion shall sign and date the informed consent. Where required, a witness shall sign and personally date the informed consent.

A copy of the signed informed consent shall be given to the subject. The other original signed consent shall be archived in the Investigator's File at the investigational site, according to the requirements of the country's health regulations, but for at least 2 years after shipment and delivery of the last device for study use and FDA/health authorities or regulatory agencies have been notified of study closure.

The subject or the subject's legally authorized representative shall be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the clinical investigation. The communication of this information shall be documented.

In circumstances where the subject is unable to give informed consent (e.g. surgical complications requiring the use of a back-up CI422 device), the informed consent of the subject's legally authorized representative, if present, shall be requested.

14.2 Confidentiality

In accordance with Good Clinical Practices (GCPs) and with the Health Insurance Portability and Accountability Act of 1996 ("HIPAA") all information concerning the subjects in the study must be treated as strictly confidential by all persons involved in the study. The investigator acknowledges that any and all information acquired from the Sponsor or its designee or developed or acquired in connection with the study are strictly confidential. The investigator will not disclose any confidential information to any third party nor use confidential information for any purpose without first obtaining the consent of Sponsor in writing. Such consent shall be deemed to have been given for disclosure to any person for whom the investigator is responsible at his/her center, but only so far as required for the purposes of the study, and, in the case of disclosures to staff, only if such staff are bound by obligations of confidentiality no less strict than those set out herein.

15 PROTOCOL AMENDMENTS AND DEVIATIONS

The Sponsor will document modifications to the protocol in the form of a written amendment. Protocol modifications that impact subject safety or the validity of the study must be approved by the FDA and IRB before implementation.

A protocol deviation refers to a study-related activity that is not in compliance with the investigational protocol. Deviations that are required to protect the life or well-being of a subject do not require prior approval from the Sponsor and should be implemented immediately. The IRB and Sponsor must be notified within 5 (five) days of the event.

If a subject is unable to return for follow-up before the closure of a study visit window (+/- 30 days for post-activation study visits), or if protocol defined assessments or parts thereof are omitted or completed incorrectly, the event is to be noted on the Protocol Deviation Log provided to the Investigator in the study Regulatory Binder. Depending on the type or severity of the deviation the Investigator may be required to notify the IRB and/or Sponsor if the deviation impacts safety or performance of the subject or data integrity.

16 DATA MANAGEMENT

Data collection is performed through electronic data capturing (EDC) on eCRFs. All study data will be entered into an Electronic Database Capture (EDC) system. Site personnel will be trained on the completion of the eCRFs prior to obtaining 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. Sponsor's 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)."

The data quality assurance tool has been designed as an automatic feature of the EDC system. When a form is submitted the system conducts instantaneous validation and cross-form validation checks. A query is generated 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. Upon request investigators will be provided with site specific data (e.g. on a CD-ROM) for national and site specific archiving requirements. After the final progress report has been approved by the agency, the data are maintained with the trial master file at the sponsor's site. The data are stored for at least 2 years after shipment and delivery of the last device for study use and FDA/health authorities or regulatory agencies have been notified of study closure.

In addition to the data collected on the eCRF, data is also to be collected through the clinical fitting software. The file records shall be anonymized and unique alphanumeric code will identify the subject throughout the course of the study. For example, US01-532-0000, where:

- US = United States
- 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,
- 532 = an abbreviation for the study, in this case 532 for the CI532 implant,
- 0000 = a unique, numeric study site identification.

17 DEVICE ACCOUNTABILITY

Study devices will be shipped with individual registrations cards indicating the study number. Devices should be registered by the clinic according to usual practice.

18 VULNERABLE POPULATION

Not applicable for this clinical investigation.

19 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 the FDA, the Investigator will contact the Sponsor or its designee immediately. The Investigator will also grant Sponsor representatives the same privileges offered to FDA/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 IRB. Renewals, with continuance of the study, must be submitted at yearly intervals or as required by IRB policy and a copy of the approved and dated renewal provided to the Sponsor.
- A copy of the IRB approved informed consent form along with any modifications initiated by the Sponsor over the course of the study.
- An IRB 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 IRB 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 AE reports submitted to the Sponsor.
- Copies of all FDA progress reports submitted to the site by the Sponsor.
- Site Delegation Signature Log.

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.

20 PUBLICATION POLICY

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law.

The aggregate data resulting from this study will be the proprietary information of the Sponsor and may be made public after all data have been analyzed and the study results are available. None of the data resulting from this study will be allowed to be presented or published in any form, by the Investigator or any other person, without the prior written approval of the Sponsor.

The responsibility for writing the publication lies with the Principal Investigator. The publication shall be reviewed by the sponsor at least 30 days in advance to any release of publication. If the publication contains information that the sponsor at his discretion finds worth protecting in the form of a patent or trademark etc., the sponsor has the right to delay the publication or presentation.

21 CHANGE HISTORY

Version	Change	Author	Date

22 DEFINITIONS

22.1 Definitions from ISO 14155:2011

Term	Description
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 investigational medical device. 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. NOTE 3 For users and other persons, this definition is restricted to events related to investigational medical devices.
Adverse device effect (ADE)	Adverse device effect is an adverse event related to the use of an investigational medical device. Note to the author: NOTE 1 This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. NOTE 2 This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
Device deficiency (DD)	A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. NOTE Device deficiencies include malfunctions, use errors, and inadequate labelling.
Incident	Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a subject, or USER or of other persons or to a serious deterioration in their state of health.

Term	Description
Serious adverse event (SAE)	A serious adverse event is any adverse event that: a) led to a death, b) led to a serious deterioration in the health of the subject that either resulted in 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient hospitalization or prolonged hospitalization, or 4) 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)	A serious adverse device effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated serious adverse device effect (USADE)	An unanticipated serious adverse device effect is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the risk analysis report (for the investigational device or its comparator).

22.2 Other definitions

Term	Description
CA	Competent Authority
CER	Clinical Evaluation Report
EC	Ethics Committee
IB	Investigator's brochure is a compilation of the current clinical and non-clinical information on the investigational device(s) relevant to the clinical investigation.
ITT analysis	The comparison of the treatment groups for all subjects as originally allocated after randomisation to avoid bias.
NCA	National Competent Authority
PASS	Post-authorization safety studies mandated by medical device regulators
PIC	Patient Informed Consent form
PIL	Principal Investigator List
PMS	Post-market surveillance studies

Term	Description
PP analysis	The comparison of treatment groups that includes only those subjects who completed the treatment originally allocated according to the protocol (i.e. a complete dataset). This form of analysis is open to bias is it does not include comparison of treatment groups for all subjects enrolled into the investigation.

23 REFERENCES

23.1 Internal References

ID	Document Title	Number

External Reference List

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