Cochlear

PROTOCOL

Implantation with the Cochlear Nucleus® CI532 Implant

Early Experience Study

March 31, 2016

Study Sponsor:

Cochlear Americas

13059 E. Peakview Avenue,

Centennial, CO 80111

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, "**Implantation with the Cochlear Nucleus® CI532 Implant - Early Experience Study.**

Clinical Investigational Site

Primary Investigator's Name (print)

Title

Signature

Sponsor Representative

Title

Signature

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Clinical Investigational Synopsis

Title	Implantation with the Cochlear Nucleus® CI532 Implant Early Experience Study
Study Sites	Up to 15 study sites
Study Duration	3 months post-activation (per subject)
Study Population	Up to 50 newly implanted cochlear-implant recipients
Design Overview	The design is a within-subject, repeated-measures study. The period of participation will be 3 months postactivation. Study procedures will include mapping, speech perception, and questionnaires.
Primary Objectives	1. To determine if unilateral listening performance at 3 months post activation with the CI532 will be superior to the best aided unilateral preoperative condition for sentence perception in quiet. 2. To determine if unilateral listening performance at 3 months post activation with the CI532 will be superior to the best aided unilateral preoperative condition for sentence perception in noise.
Primary Endpoints	1. Sentence perception in quiet will be superior for subjects implanted with the CI532 when compared to their preoperative best aided unilateral listening condition. 2. Sentence perception in noise will be superior for subjects implanted with the CI532 when compared to their preoperative best aided unilateral listening condition.
Additional Information	1. To quantify the change in audiometric threshold (125 – 750 Hz) at 3 months postactivation when compared to the preoperative period
Study Intervals	Primary data points are at 3 months post-activation.

Abbreviations

Term	Definition
AE	Adverse Event
CRF	Case Report Form
IA	Initial Activation
IRB	Institutional Review Board
SAE	Serious Adverse Event
SNR	Signal to noise ratio
S_0N_{90}	Speech presented at 0 degrees azimuth and background noise presented from the side of the implant

1. Introduction

Cochlear implantation is an FDA and Health Canada approved treatment for sensorineural hearing loss. Nucleus cochlear implants are indicated for individuals who demonstrate minimal benefit from appropriately fit hearing aids. Audiometrically, adults must possess a bilateral moderate to profound sensorineural hearing loss and children must possess a severe to profound sensorineural hearing loss. A common hypothesis in peer reviewed literature is that performance outcomes with cochlear implants depend critically on the placement of the electrode array within the cochlea.

A cochlear implant is composed of two main components: a receiver stimulator and an electrode array. Electrode array designs are typically either lateral wall or peri-modiolar hugging. A lateral wall electrode is a straight electrode design that, when inserted into the cochlea, hugs the outer wall of the cochlea, with final position *lateral* to the modiolus. A perimodiolar electrode is a pre-curved electrode design, held straight for insertion purposes, but as inserted into the cochlea curves to mimic the curvature of the modiolus, with final position medial to the modiolus. Electrode placement closer to the modiolus has been documented to improve performance outcomes in traditional cochlear implant candidates (Holden et al. 2013; van der Beek et al. 2005).

In addition to medial and lateral placement, there are also scala considerations within the cochlea. The cochlea is divided into three scala: scala media, scala tympani and scala vestibuli. Holden et al (2013), Finley et al. (2008), Aschendorff et al. (2007), Skinner et al. (2007) as well as other peer reviewed publications have demonstrated that electrode arrays located within scala tympani, as opposed to scala vestibuli, are often correlated with higher speech perception scores. Due to the location of ganglion cells within the modiolus, it has been suggested that there is a higher potential for electrodes in scala vestibuli to stimulate more than one turn of the cochlea, potentially causing cross-turn stimulation, pitch confusions and therefore diminished speech recognition (Finley et al. 2008).

The device proposed for study is the Nucleus® CI532 cochlear implant which consists of a CI500 Series receiver/stimulator and a pre-curved, modiolar electrode array (EA32). Individuals who will be recruited for participation in this study will be required to meet commercial cochlear implant indications. The study will compare the performance outcomes at 3 months postactivation with the best aided preoperative performance outcomes using a within subject study design. Up to 15 clinical study sites will be asked to participate with up to 50 subjects implanted.

2. Study Objectives

2.1 Primary Objectives:

1) To determine if performance at 3 months post activation with the CI532 is superior to the best aided unilateral preoperative condition for sentence perception in quiet.
2) To determine if performance at 3 months post activation with the CI532 is superior to the best aided unilateral preoperative condition for sentence perception in noise.

2.2 Primary Endpoints:

1) Sentence perception in quiet will be superior for subjects implanted with the CI532 when compared to their preoperative best aided unilateral listening condition.
2) Sentence perception in noise will be superior for subjects implanted with the CI532 when compared to their preoperative best aided unilateral listening condition.

3. Study Design

The design is a within-subject, repeated-measures clinical investigation.

4. Study Length

The duration of the study for each subject is 3 months post-activation.

5. Device Description

The cochlear implant system that will be used in this study comprises:

- Nucleus® CI532 Cochlear Implant
- Nucleus 6 (CP900 series) Sound Processor, and
- Nucleus Custom Sound™ programming software.

5.1 Implant Description

The commercially available Cochlear Nucleus CI532 cochlear implant will be used in this study.

Figure 1. Nucleus CI532 cochlear implant.

5.2 Sound Processor Description

The commercially available Nucleus 6 sound processor will be used in this study.

Figure 2. Nucleus 6 (CP900 series) sound processor.

5.3 Programming Software Description

The commercially available programming software, Custom Sound, will be used in this study.

6. Subject Population

6.1 Inclusion Criteria

- Medical and audiological candidate for a CI532 cochlear implant per commercially approved, age appropriate, FDA indications
- Post-linguistically deafened
- Ability to complete age appropriate testing

6.2 Exclusion Criteria

- Previous cochlear implantation in the ear to be implanted
- Pre-linguistically deafened (onset of hearing loss at less than two years of age)
- Women who may be pregnant at the time of cochlear implant surgery
- Ossification or any other cochlear anomaly that might prevent complete insertion of the electrode array
- Diagnosis of retro-cochlear pathology
- Diagnosis of auditory neuropathy
- Unrealistic expectations on the part of the subject regarding the possible benefits, risks, and limitations that are inherent to the surgical procedure and use of the prosthetic device
- Unwillingness or inability to comply with all investigational requirements
- Additional cognitive handicaps that would prevent participation on all study requirements

6.3 Release of Medical Information

Subjects will be required to release the exchange of medical information between the Investigator(s) and the Sponsor. This requirement will be clearly identified in the Informed Consent form.

7. Investigational Procedures

7.1 Design Overview

The Implantation with the Cochlear Nucleus® CI532 Implant - Early Experience Study will be conducted as a multi-center, prospective, single-arm clinical study, evaluating the safety and functionality of the Cochlear Nucleus CI532 cochlear implant in up to 50 subjects who meet current cochlear implant indications. 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.

7.2 Description of Test Measures

7.2.1 Clinical Audiological Testing

Subjects will undergo a standard battery of audiological tests. Audiological data will be gathered pre-operatively, at Initial Activation (IA) and at 3-months post IA.

The clinical data gathered for this study will include:

1) Tympanometry, both ears.
2) Frequency-specific thresholds at standard audiometric frequencies for both ears.
   a) Air conduction: 125, 250, 500, 750, 1000, 2000, 3000, 4000, and 8000 Hz
   b) Bone conduction: 250, 500, 1000, 2000, 3000 and 4000 Hz
3) Aided speech recognition in quiet: AzBio sentences (Spahr et al., 2012) presented at 60 dBA in the sound field for the unilateral listening ear.
   a) Sentence testing in quiet will only be conducted in subjects aged 12 years and older
4) Aided speech recognition in noise: AzBio sentences (Spahr et al., 2012) using speech weighted noise presented at 65 dBA with a +5 dB signal to noise ratio spatially separated, speech 0 degrees azimuth and noise 90 degrees towards the implanted ear.
   a) Sentence testing in noise will only be conducted in subjects aged 12 years and older.

Note: The contralateral ear will be plugged/muffed for all audiological testing.

7.2.2 Device Fitting

Mapping will be conducted using standard clinical procedures using Custom Sound default program settings for the Nucleus 6 sound processor.

7.3 Preoperative Procedures

7.3.1 Visit 1

A baseline evaluation will be conducted to measure the subject's preoperative, best aided, unilateral listening performance pre-surgery. The following audiological testing will be completed:

1) Tympanometry, both ears.
2) Frequency-specific thresholds at standard audiometric frequencies for both ears.
   a) Air conduction: 125, 250, 500, 750, 1000, 2000, 3000, 4000, and 8000 Hz
   b) Bone conduction: 250, 500, 1000, 2000, 3000 and 4000 Hz
3) Aided speech recognition in quiet: AzBio sentences (Spahr et al., 2012) presented at 60 dBA in the sound field for the unilateral listening ear.
   a) Only to be collected on subjects aged 12 years and older.
4) Aided speech recognition in noise: AzBio sentences (Spahr et al., 2012) using speech weighted noise presented at 65 dBA with a +5 dB signal to noise ratio spatially separated, speech 0 degrees azimuth and noise 90 degrees towards the implanted ear for the unilateral listening ear.
   a) Only to be collected on subjects aged 12 years and older.

7.4 Intraoperative Procedures

7.4.1 Visit 2

There are no modifications to the standard surgical procedure for this study.

All surgeons will be required to complete a surgical questionnaire for each implanted subject. Intraoperative measures (impedance and NRT) are optional.

Additionally, intraoperative imaging (plain film x-ray) is recommended but not required, consistent with the Cochlear Nucleus CI532 Surgeons Guide.

7.5 Postoperative Procedures

7.5.1 Visit 3

At the initial activation appointment, the following procedures will be completed:

1) Tympanometry, both ears.
2) Frequency-specific thresholds at standard audiometric frequencies for both ears.
    a) Air conduction: 125, 250, 500, 750, 1000, 2000, 3000, 4000, and 8000 Hz
    b) Bone conduction: 250, 500, 1000, 2000, 3000 and 4000 Hz
3) The initial activation will be performed according to standard clinical procedures using Custom Sound and the default programming settings for the Nucleus 6 sound processor.
    a) Impedances and NRT are to be measured.
    b) An anonymous .cdx file will be provided to the study sponsor.
4) Audiologist Questionnaire will be completed for each subject.

7.5.2 **Visit 4**

At 3 months postactivation, the following procedures will be completed:

1) Tympanometry, both ears.
2) Frequency-specific thresholds at standard audiometric frequencies for both ears.
    a) Air conduction: 125, 250, 500, 750, 1000, 2000, 3000, 4000, and 8000 Hz
    b) Bone conduction: 250, 500, 1000, 2000, 3000 and 4000 Hz
3) Aided speech recognition in quiet: AzBio sentences (Spahr et al., 2012) presented at 60 dBA in the sound field for the unilateral listening ear.
    a) Only to be collected on subjects aged 12 years and older.
4) Aided speech recognition in noise: AzBio sentences (Spahr et al., 2012) using speech weighted noise presented at 65 dBA with a +5 dB signal to noise ratio spatially separated, speech 0 degrees azimuth and noise 90 degrees towards the implanted ear for the unilateral listening ear.
    a) Only to be collected on subjects aged 12 years and older.
5) Mapping will be performed according to standard clinical procedures using Custom Sound and the default programming settings for the Nucleus 6 sound processor.
    a) Impedances and NRT are to be measured.
    b) An anonymous .cdx file will be provided to the study sponsor.

7.6 Summary of Data Collection Visits

	Visit 1	Visit 2	Visit 3	Visit 4
Test	**Baseline**	**Surgery**	**Initial Activation**	**3 Mos Post Activation**
Informed Consent	X			
Tympanometry	X		X	X
Audiometric	X		X	X
AzBio Quiet	X*			X*
AzBio Noise	X*			X*
Surgical Questionnaire		X		
Intraoperative Testing		X (optional)		
Imaging		X (optional)		
Audiological Questionnaire			X	
Device Programming (.cdx)			X	X

*Note for subjects aged 12 years and older.

8. Adverse Events

An adverse event (AE) is any undesirable clinical or medical occurrence associated with the use of the device, procedure, or participation in the study, which does not result in serious injury or illness related to the surgical procedure or the device.

A serious adverse event (SAE) is any untoward medical occurrence that

- results in death
- is life-threatening

- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- requires medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
- leads to fetal distress, death, or congenital abnormality or birth defect
- is a medically important event or reaction

8.1 Assessment and Reporting of Adverse Events

To monitor subject safety throughout this study, any procedure or device related adverse events will be recorded. Information on all adverse events will be maintained by event type. The investigator will complete an Adverse Event form if any adverse event is reported or observed for a subject during this study, even if the event was acknowledged as a risk factor in the Informed Consent form.

Adverse device effects refer to any undesirable clinical or medical occurrence associated with use of the device or participation in the study. Any/all adverse device effects are to be recorded via the Adverse Event form. Adverse device effects will be reported if observed, even if they were acknowledged as risk factors in the Informed Consent form.

8.2 Unanticipated Adverse Device Effects

Unanticipated adverse device effects refer to any event not identified above that represents a “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, 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)]

Investigators are to inform their respective Institutional Review Boards (IRBs) and Cochlear Americas immediately if an unanticipated adverse device effect is suspected (no more than 10 working days after the investigator learns of the effect). If the case is determined to be an unanticipated adverse device effect, the investigator will fill out an “Unanticipated Adverse Device Effect Form.” Cochlear Americas will report the results of an evaluation of the unanticipated adverse device effect to all reviewing IRBs and investigators within 10 working days after first receiving notice of the event.

9. Study Completion

9.1 Completed Subjects

Once the 3 month postactivation visit is completed, the subject will be deemed complete. Subjects will continue to receive standard clinical follow-up care at their cochlear implant facility after the study.

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
- Investigator decision
- 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 and IRB.

During surgery, an alternative device (e.g., CI522 or CI512) may be implanted in subjects where there are difficulties with the CI532. These subjects will be discontinued from the study.

Subjects who withdraw or are discontinued prior to the completion of the 3 month visit will receive compensation of $12.50/ hour for the cumulative period of time spent on study procedures.

9.3 Premature Study Termination

The Sponsor may terminate the study early in the case of major non-adherence to the protocol, or if it is anticipated that recruitment will not be met for the required number of subjects to complete the study objectives. In the event of premature study termination, the subjects who are already enrolled will be sponsored through study completion.

10. Data Analysis

10.1 Statistical 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 CI532 and completed per the protocol will be considered as the completed cases (CC) population and per protocol (PP).

Demographic and outcomes data will be tabulated individually along with group summary descriptive statistics. Speech perception scores will be presented for each study evaluation, pre- and postoperatively, so that postoperative progress can be evaluated over time.

Performance with the Nucleus CI532 will be determined by a comparison of preoperative, best aided, ear to be implanted vs. 3 months postactivation outcome measures. The speech perception measures chosen for this purpose are the AzBio sentences in both quiet and noise in the unilateral listening condition.

The primary study endpoints will be statistically significant differences between the mean, preoperative speech perception scores and postoperative scores for the activated, CI532 cochlear implant subjects who completed speech perception testing. Mean scores as measured by AzBio sentences in quiet and noise will be compared. The null hypothesis to be tested is that there is no difference for the subjects between their pre- vs. postoperative speech performance

Individual scores obtained at 3 months will be compared with those obtained, on the same measures preoperatively, based on the binomial model where appropriate (see Thornton and Raffin, 1978; Boothroyd and Nittrouer, 1988). Although the binomial model is the more appropriate statistical model for analysis of single-subject experimental data, conventional group-based statistics will also be applied to the pooled results. For all of the speech perception measures, nonparametric procedures (e.g., a Signed-Ranks test) will be conducted in order to further confirm the results of the single-subject analyses. These tests will be two-tailed and applied using an alpha level of 0.05.

10.2 Sample Size

The proposed study is designed to collect performance data associated with CI532 cochlear implantation. Based on the preliminary 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 a minimum of 25 subjects to be recruited into the study and implanted. In effort to enroll subjects 12 years and under who are unable to complete speech perception for primary endpoint testing and have more than 3 subjects per site, the sample size has been increased to up to 50 subjects.

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 six months to recruit up to 50 subjects. The enrollment period may be extended if required.

11. Risk Benefit Statement

11.1 Benefits

It is possible but not guaranteed that advances to cochlear implant technology will improve performance or usability of devices for future recipients. This investigation will help to inform the future development of potentially new electrode designs and the planning of future studies in the newly implanted population. There are no direct benefits anticipated for subjects participating in this study.

11.2 Risks

It is expected that the risks associated with the procedure to place the cochlear implant are no greater than those associated with cochlear implantation in general. Cochlear implantation is an accepted treatment option for adults with bilateral moderate (for low frequencies) to profound sensorineural hearing loss.

With any cochlear implant mapping, there is a very small risk of unintentional over-stimulation. Subjects may experience sounds during mapping that are uncomfortably loud.

12. Good Clinical Practices Statement

The study obligations for the Investigator(s) are outlined in guidelines for Good Clinical Practice (GCP), ISO14155:2011 (Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice), and the Declaration of Helsinki.

13. Access to Study Documents and Study Monitoring

Investigator(s) will provide access to study documentation including source data for the purposes of monitoring, audits, IRB review, and regulatory inspections.

14. Quality Control and Assurance

Study sites may be subject to Quality audits at any point during the study. Regulatory agencies may conduct inspections during the course of the clinical investigation and after study completion.

15. Institutional Review Board

Each site will obtain approval from its designated IRB prior to commencing any study-related activities. A copy of the IRB approval will be kept in the Investigator file(s). Any additional requirements imposed by the IRB and/or regulatory authority shall be followed. The Investigator(s) will submit the appropriate documentation if any necessary extension or renewal of the IRB approval must be obtained.

16. Informed Consent Process

Written informed consent shall be obtained from each subject after explaining the rationale for and the details, aims, and objectives of the study, the risks and benefits of the trial treatment (and alternative treatments), and the extent of the patient's involvement. The Investigator is responsible for ensuring that all patients give written informed consent prior to any study-related examination or activity. All patients shall sign and date the Informed Consent Form, and a copy of the Informed Consent Form shall be given to the patient.

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.

17. Confidentiality

A Case Report Form (CRF) will be completed for each study subject, summarizing all clinical and study data. The CRF contains confidential material. Subjects will only be referred to in the CRF by their subject numbers in order to retain subject confidentiality. Specific instructions to complete the CRF shall be provided to the clinical investigation team as appropriate.

Copies of the completed CRFs are to be provided to the Sponsor as soon as practical after completion and review. The original CRFs are to be retained by the Investigator for a period of time as determined by local regulations.

18. Protocol Deviations and Amendments

The Investigator must receive prior approval from the Sponsor, and the IRB when necessary, to deviate from the protocol except in cases of emergency to protect the rights, safety, and well-being of the subjects. Emergency protocol deviations must be documented and reported to the Sponsor and the IRB.

Study procedures will not be changed without mutual agreement between the Sponsor and the Investigator(s). Changes will be implemented in a signed protocol amendment, and for significant changes, approval will be obtained from the IRB.

19. Data Management

Data will be recorded on electronic CRFs within the electronic data capture system DataLabs™. DataLabs will produce a report of the summary data per subject. Source data for study evaluations may include paper worksheets or electronic spreadsheets. All source data will be stored in subject binders or on password-protected computers. The study monitor will compare the DataLabs CRFs with the source data.

20. Record Keeping and Retention

All source documents, CRFs, and trial documentation will be kept by the Investigator(s) for the appropriate retention period as stipulated by local regulations and ICH-GCP.

21. Study Report and Publication

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. At the end of the study, a clinical study report will be written by the study Investigators or their designee and reviewed by the Sponsor.

22. References

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