CLINICAL PROTOCOL
MEDICAL DEVICE INVESTIGATIONAL PLAN

PIVOTAL STUDY
Efficacy clinical trial

Application Title: The Neuro Zti Cochlear Implant System Efficacy and Safety in Adults
Device Name: Neuro Zti Cochlear Implant System
Sponsor: Oticon Medical, Dan GNANSIA 2720 Chemin Saint Bernard 06224 Vallauris France
Internal Ref: PIC_07
Version and date: Version G, February 2019

History

Version	Date	Reason(s)	Written by
A	April 2016	Creation	S. SAAÏ
B	May 2016	Precision and Change on statistics methodology. Sensitivity analysis. Sample size determination.	S. SAAÏ
C	June 2016	Visit interval modification from -4 to -8 weeks for V1 with interval windows modification from 14 days ± 2 days to 28 days ± 14 days from V1. Visit interval modification from -2 to -6 weeks for V2 with interval window modification from 14 days± 2 days to 28 days ±14 days from V2. Change on §3.3.2 study design. Precision on the inclusion criteria (3) PTA ≥ 70db HL, average in db of the thresholds for pure tones at 500, 1000 and 2000Hz on both ear. ICF pages (Appendix 2) translate from French to English. Team study list removed, from p6-7 and moved to the SMF.	S SAAÏ
D	July 2016	Appendix 7 "CRF" removed SAE form: email dagn@oticonmedical.com added. Appendix 2 "ICF" Protocol version removed AND title rectification "The Neuro Zti Cochlear Implant System Efficacy and Safety in Adults" instead of "The Neuro Zti Cochlear Implant System Performance in Adults"	S SAAÏ
E	August 2016	Inclusion criteria: - Definition of post-lingual added - "Open-set sentences" completed by "HINT sentences" Adaptive HINT-N modified to HINT-N at +10dB SNR with fixed signal and fixed noise. HINT-N baseline added and secondary objectives updated consequently. Section 3.5.5.1, section 3.5.5.4 and section 3.5.7 (Visit 2), section 3.6.1.2 updated. Appendix 7 removed from protocol. Statistical Analysis reviewed, with site effect added and language effect comparison removed to language trends comparison and secondary objectives updated consequently. Study planning delayed by 3 months. Cable lengths modified from 3 to 2, page 67. Appendix 2, procedure updated with HINT-N in ICF.	S SAAÏ
F	October 2017	Inclusion period: 13 month Revised Danish and French speaker participants number	S SAAÏ

		Visit interval modification for V2 with interval window from 28 days (+/14 days) to 28 days (-25 to +14 days) from V1 Pure Tone Audiometry can be performed within 6 months before the visit 2 (inclusion visit) Tympanometry can be performed within 6 months before the visit 2 (inclusion visit) Typo : 3.5.7 Visual analog pain scale deleted from visit 4 Typo : 3.6.1.1 HINT 6 months following activation corrected AE form E2 - 18jan2017 implemented (appendix 3) SAE form E2 – 18jan2017 implemented (appendix 4) Patient Hint Performance Memo added (appendix 7) Post-operative ECAP Measurement added (appendix 8) Calibration considerations added (appendix 9)	
G	February 2019	Start date updated Inclusion period extended Completion date postponed	S SAAÏ

STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Conference on Harmonization guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46). All personnel involved in the conduct of this study have completed human subjects' protection training.

PROTOCOL SIGNATURE PAGE

Sponsor representative

The sponsor makes a commitment to realize this study according to all legal and statutory measures of which the research and according to the protocol could recover.		
Name	**Date :**	**Signature :**
	14 th Feb. 2019	SAAI

PROTOCOL AGREEMENT

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator or Clinical Site Investigator:

Signed: _____ Date: _____

Name: _____

Title: _____

Site # _____

Site Name _____

Address _____

_____

_____

_____

Phone Number _____

CONTENT

0. GLOSSARY AND ACRONYMS

AAMI	Association for the Advancement of Medical Instrumentation
BTE	Behind The Ear (sound processor)
CA	Competent Authority
CI	Cochlear Implant
CIS	Cochlear Implant System
CRA	Clinical Research Associate
CRF	Case Report Form
CSP	Cumulative Survival Percentage
DSMP	Data and Safety Monitoring Plan
EC	Ethical Committee
ECAP	Electrically-evoked Compound Action Potential
EEC	European Economic Community
FAS	Full Analysis Set
GCP	Good Clinical Practice
HINT	Hearing In Noise Test
HIPPA	Health Insurance Portability and Accountability Act of 1996
HL	Hearing Level
ICH	International Conference of Harmonization
IFU	Instructions For Use
OUS	Outside of United States
PMS	Post Market Surveillance
PPS	Per Protocol Set
PHI	Protected Health Information
PI	Principal Investigator
PTA	Pure Tone audiometry
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAS	Safety Analysis Set
SNR	Signal Noise Ratio
SPL	Sound Pressure Level
SRT	Speech Reception Threshold
SSID	Subject Single Identifier
USADE	Unanticipated Serious Adverse Device Effect

1. SUMMARY

Title	"The Neuro Zti Cochlear Implant System Efficacy and Safety in Adults"
Sponsor	Oticon Medical
Investigator Coordinator	Dr. David Schramm (Canada)
Phase and Design	Multinational, multicenter, prospective, open label, single arm.
Study description	The new cochlear implant system (CIS) is indicated in individuals with serious hearing disabilities who do not obtain benefit from appropriately fitted hearing aid(s). Cochlear implant surgery is safe, but as with any surgery, possible issues or device related issues may occur. The risk benefit balance is well known in cochlear implantation. The aim is to assess the efficacy and the safety of this new CIS in adults.
Primary objectives	To demonstrate the efficacy of the new CIS through improvement of speech performance in quiet conditions after CIS implantation. To evaluate the safety of the CIS.
Secondary objectives	To assess the device effect with speech performance in noise. To show sustainability of the device effect in quiet and in noise in time and after 12 months of use. To assess whether the time of course of the response follow the same tendencies (increase, decrease, slope inversion) in the three languages in quiet and noise conditions.
Primary endpoints	HINT score in quiet (HINT-Q) at 6 months of device use. Major complications incidence rate at 12 months of device use.
Secondary endpoints	HINT in noise (HINT-N) scores at 3, 6 and 12 months of device use HINT-Q scores at 3 months and at 12 months, Electrodes impedance at each visits ECAP at each visit
Inclusion & exclusion criteria	Inclusion: - ≥ 18 y.o., - Bilateral severe-to-profound sensorineural hearing loss, - Post-lingual deafness - Limited benefit from appropriately fitted hearing aid(s), - Primary implantation, - No anatomic contraindications, - Fluent in local language, Exclusion: - Medical conditions that contraindicate undergoing surgery, - Psychologically unsuitable, - Unwillingness or inability to comply with all investigational requirements.
Investigational medical device	Neuro CIS, with Neuro Zti implant and Neuro One processor
Study planning	Start date: January 2017 Inclusion period: 23 months Running period: 14 months (1 month eligibility period + 13 months postoperative follow-up) Completion date: December 2019
Number of subjects planned	39 English-speaking subjects to assess the primary endpoint with additionally 16 non-English (8 Danish and 8 French) speaking

	subjects to assess safety. In case of shortage of recruitment in a given language recruitment can be increased in another language provided that a minimum of 5 French and 5 Danish speaking patients should be implanted.
Number of centers	5 in Canada, 1 in Denmark
Statistical analysis	Primary efficacy analysis based on the English speaking patients the primary efficacy endpoint (change from baseline to M6 of the HINT-Q) and a one sample t test. Mixed Model for repeated measures with appropriate contrasts.

2. PURPOSE OF THE INVESTIGATION

2.1 Introduction

The gold standard for treating permanent hearing impairment is the cochlear implant (CI); this constitutes the most widely used therapeutic surgical intervention in patients with a sensorineural bilateral severe-to-profound hearing loss. As of December 2012, approximately 324,200 cochlear implants have been implanted worldwide, in the United States roughly 58,000 devices have been implanted in adults and 38,000 in children [1,2]. It is estimated that nearly 30,000 additional devices have been implanted in the United States since the 2012 report and it is estimated that the number of implantees worldwide now exceed 500,000 CIs.
Balkany et al. [6] reported a HINT score in quiet increase from 11.3±25.6% to 78±24.9%) on 55 patients at the 6-month follow-up. Similar results were reported by Bradley et al. [8] with a speech intelligibility change from 14±17% to 75±28% at 6 months in the same material. Waltzman et al. and Lin et al. express their results in mean increase HINT score in quiet from pre- to post-implantation which are 47.7±26.6% and 60±24.1% respectively [42,43].

Large investments in research and development as well over 30 years of clinical experience have established that cochlear implants are safe and clinically effective. The FDA initially approved CIs for adults in 1984, however the benefits provided by CIs have led to the extension of indications in 2000 to children 12 months and older. In addition to CIs, the tremendous expansion of the field of neuromodulation leveraging electrical stimulation via implantable electrodes (i.e. spinal cord stimulation, deep brain stimulation, vagal nerve stimulation) as well as the long term electrical stimulation for cardiac rhythm management have further established the safety of long term electrical stimulation of biological tissues in millions of patients worldwide.

CISs have been shown to improve sound perception and speech understanding with associated risks including those related to the surgery itself and related to the device. The major post-surgical complication rate is 6.8% patient-years in children and 1.4 to 1.7% in adults. The minor complication rate is 34.7% and 35.3% patient-years in children and adults, respectively [12]. In addition, there are risks that other adverse events associated with the implant could occur, such as mechanical or electrical failure, rejection, infection and problems that require device explant and/or device replacement. Despite the aforementioned risks, CIs have been proven to be reliable; according to the reliability reports of the four largest manufacturers of CIS the cumulative survival percentage (CSP) of implanted components range from 97.37% after 9 years (Digisonic SP), 98.09% after 8 years (HiRes 90K), 98.29% after 8 years (Sonata), 99.1% after 11 years (CI24RE) (manufacturers reliability reports, 2015 [13,14,15). The literature review gives an weighted average of major complication of 7.09% ± 2% [16,17,18,19,20,21].

Given the historical data, including prior FDA approvals of CIS produced by three different manufacturers, the risk/benefit balance is favorable, indicating that cochlear implantation can be a safe and effective treatment for severe-to-profound deafness in adults and children.

Oticon Medical has developed a new CIS named “The Neuro Cochlear Implant System” which consists of an implantable part (Neuro Zti) and an external part (Neuro One). The Neuro One detects and processes sound and is designed to be worn behind the ear (BTE). The Neuro Zti is designed to be surgically implanted and consists of the receiver/stimulator which is implanted under the skin on the temporal aspect of the skull and a multichannel electrode designed to be

placed within the Scala Tympani of the cochlea enabling direct electrical stimulation of the spiral ganglion. All power and data are transmitted from the Neuro One to the Neuro Zti via an inductively coupled transcutaneous link.

This pivotal study will assess the Efficacy and the Safety of the CIS in adults with severe to profound bilateral hearing impairment, across Europe and Canada. It is hypothesized that sentence recognition at normal conversational levels in quiet conditions is better at 6 months of device use that at baseline and the risks of complications associated with the implanted components is similar to those observed in data from literature.

2.2 Name of the Investigational Device

Generic name: Cochlear Implant System
Commercial name: Neuro Cochlear Implant System

The "Neuro Cochlear Implant System" is the investigational device to be studied and includes the internal and external parts of the system. The internal/implanted part is designated as Neuro Zti, and external part as the Neuro One sound processor.
The Neuro CIS is CE and Health Canada approved.

2.3 Intended Use of the Investigational Device

The Neuro Cochlear Implant System is intended to provide the opportunity to detect and recognize auditory information through electrical stimulation of the auditory nerve for patients with severe to profound bilateral sensorineural hearing impairment, and who obtain limited benefit from appropriately fitted hearing aid(s).

The Neuro CIS is foreseen in the following conditions:

- Adults of 18 years old or older with a bilateral, pre- or post- linguistic, sensorineural severe to profound deafness and obtain a limited benefit from appropriately fitted hearing aid(s). The hearing impairment is determined by a pure tone threshold ≥ 70 dB HL from and including 500 Hz. Limited benefit from hearing aid(s) is determined to be a score of 50% correct or less in the best-aided condition on an established calibrated recorded test of open sentence recognition.

- Children[1] aged 12 months to 17 years old, having a profound bilateral hearing loss determined by a pure tone threshold ≥ 90 dB HL from and including 500Hz and;
    - In a young child, limited benefit is defined by a lack of auditory progress with appropriate fitting hearing aid(s) despite intensive aural rehabilitation over 3-6 months period.
    - In an older child, lack of auditory progress is defined as < 20% correct on open-set word recognition test Multisyllabic Lexical Neighborhood Test (MLNT) or Lexical Neighborhood Test (LNT), depending on cognitive ability and linguistic skills.

[1] Device intended use for the US market. Pediatric indication is not supported by this clinical trial. Pediatric indications are only indicative here and will be investigated in a next step. For this protocol, this device is to be used in a clinical investigation framework. The Neuro System is currently approved for adults and children under CE mark and Health Canada license. For specific indications within European countries please refer to the instructions for use (IFU) in the device sales packaging.

2.4 Objectives of the Clinical Investigation

Device efficacy is defined as an improvement in the speech recognition battery presented at conversational speech levels (60 dB SPL, see Appendix 9: Calibration considerations) in quiet after 6 months of use compared to the preoperative condition (best-aided pre-operative condition[2]).

Speech perception tests will be conducted

- Preoperatively, on both ear with the best fitted hearing aid(s), and
- Postoperatively, on ipsilateral ear with activated CIS and an occluded contralateral ear with ear-plug.

2.4.1 Primary objectives: Efficacy and Safety

The primary objectives are:

- To demonstrate the improvement in the speech recognition, in quiet condition, after implantation of the Neuro CIS with respect to pre-operative conditions.
- To evaluate the device safety profile and in particular the risk of complication.

Evaluation at 6 months compared to baseline will be used to determine the efficacy of the device.

The incidence rate of major complications at 12 months of device use will be estimated to evaluate the safety. Data from literature on currently similar devices FDA-approved will be used as yardsticks.

2.4.1.1 Main effect of device on speech recognition

The primary population will be composed of English-speaking subjects. In the efficacy assessment, a sub-population will be used as a primary set of patients because different languages is expected to influence the magnitude of the effect of the device.

Objective:
To assess in English speaking subjects the performance at month 6 of the device in quiet conditions compared to baseline (best-aided condition) using HINT-Q test-sentences presented at conversational level.

Hypothesis:
The mean HINT-Q score obtained with the Neuro CIS after 6 months of device use in English speaker subjects is greater than the score at baseline.

H0: $\mu_{M6} - \mu_0 \leq 0$ points
H1: $\mu_{M6} - \mu_0 > 0$ points

An improvement of approximately 50 points with respect to baseline is expected and an improvement of 20 points[3] is considered clinically pertinent.

[2] Best aided condition preoperatively: appropriately fitted hearing aids with respect to best clinical practice.
[3] PMA, Summary of Safety and Effectiveness data, Medel, Combi 40+ : http://www.accessdata.fda.gov/cdrh_docs/pdf/P000025b.pdf

2.4.1.2 Safety: Major Complications

Occurrence of major complications in all participants suffering from severe to profound bilateral sensorineural hearing loss and for whom an implantation of the device was initiated will be the co-primary objective. All surgical and device-related events will be reported and the number and proportion of major complications will be estimated.

Safety data will be collected from the preoperative visit (during surgical procedure) to the end of patient participation.

Adverse events or complications will be classified as medical/surgical or device related. Complications will be classified as major if they require surgical intervention and minor if they resolve spontaneously or with non-invasive medical treatment categories [12,22,23].
Any device failure will be investigated and classified according to AAMI-CDV-4 CI86 guideline for Cochlear Implants.

A list of adverse events is defined in section 4.2. Unanticipated adverse events (section 4.5.8) may occur (not listed in 4.2) and like anticipated events they will be reported, followed and classified.

Occurrence of major complications will be a co-primary endpoint and the presentation of the safety profile (all adverse events reported) will be a secondary objective and mainly descriptive. Incidence rate of minor and major complications will be estimated globally and per categories in order to describe the device safety profile. Data from literature on currently similar devices FDA approved will be used as yardsticks.

2.4.2 Secondary objectives

Secondary objectives are:

- To establish the time course of the change from baseline of HINT-Q score in English speaking patients and in all patients to assess the efficacy of the device in a dynamic perspective.

- To test the sustainability of the device effect in Quiet conditions (HINT-Q) through the comparison of the scores at month 6 and month 12 in English speaking patients and possibly in all patients in case of absence of significant language effect in the improvement from baseline.

- To assess the performance of device in noise using HINT-N test in English speaking and possibly in all patients at 3, 6 and 12 months compared to baseline (best-aided condition). The comparison of the score at 6 and 12 months will indicate the sustainability of the effect.

- To evaluate the trend of device efficacy in quiet and noise conditions across English speaking, French speaking and Danish speaking patients.

2.4.3 Technical functionalities

The time course from baseline of impedance values and ECAP responses amplitudes will be assessed to check device technical functionality. Mixed model will be used to assess in a dynamic perspective the objective measures evolution.

2.5 Anticipated duration of the clinical investigation

Start date: January 2017
Inclusion period: 23 months
Running period: 14 months
Completion date: December 2019

3. CLINICAL PROTOCOL

3.1 Protocol Number and Title of Clinical Protocol

Title: The Neuro Cochlear Implant System Efficacy and Safety in Adults
Protocol number: PIC_07

3.2 Protocol Version and Date

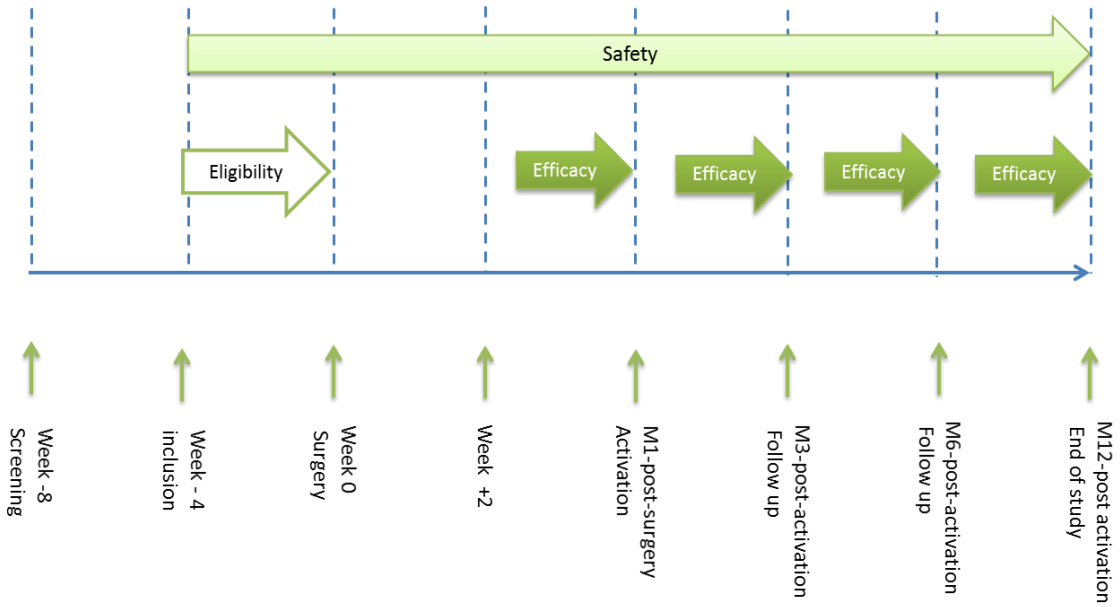
Edition G, February 2019

3.3 Study Design

3.3.1 General Study Design

This pivotal study is designed as a prospective multi-center, one arm, non-randomized, open label, repeated measures clinical study. The subjects will be their own control.

3.3.2 Study Design Schematic



3.4 Subject Selection

3.4.1 General Characteristics of the Proposed Subject Population(s)

The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

In the event of any doubt about the eligibility of a subject, the investigator should discuss the issue with the clinical study manager/clinician who will confirm whether the subject may be entered into the trial.

Adults with a bilateral severe-to-profound deafness that are existing candidates for a cochlear implant will be included in the study. Subjects enrolled will only be unilaterally implanted for the duration of the study.

Potential subjects shall be classical candidates for a cochlear implant that are referred to one of the participating cochlear implant centers. The participating center shall provide the assessment to determine whether the potential candidate is suitable for cochlear implantation. Subjects will enrolled by cochlear implant centers shall meet the eligibility criteria described in section 3.4.3 and 3.4.4.

3.4.2 Anticipated Number of Research Subjects

For the pivotal study, **55 subjects** shall be enrolled (section 3.6.1.4)

3.4.3 Inclusion Criteria

(1) Patient must understand the investigational nature of this study and sign an independent ethical committee (EC) approved written informed consent form prior to any study related activities,
(2) Must be 18 years or older,
(3) Bilateral severe-to-profound sensorineural hearing loss, PTA[4] ≥ 70 dB HL (average in dB of the thresholds for pure tones at 500, 1000 and 2000Hz, on both ear),
(4) Post-lingual[5] deafness,
(5) Limited benefit from appropriately fitted hearing aid(s), with score ≤ 50% correct in HINT sentences recognition in quiet, binaurally in the best listening condition,
(6) Primary implantation,
(7) No anatomical contraindications: Radiological evaluation showing no obstacles to full electrode insertion and verifying the absence of central auditory lesions
(8) Fluent in local language, including reading and writing,
(9) Psychologically suitable,
(10) Updated pneumococcal vaccine.

Note: Patient must understand the investigational nature of this study and sign an independent ethical committee (EC) approved written informed consent form prior to any study related activities

3.4.4 Exclusion Criteria

(1) Medical conditions that contraindicate undergoing surgery (middle ear diseases i.e. AOM/CSOM, lesions of auditory nerve, pathologies of central auditory pathway, otosclerosis any cochlear malformation (i.e. Mondini malformation, cochlear ossification, Large Vestibular Aqueduct)
(2) Unrealistic expectations from the candidate regarding the possible benefits, risks, and limitations that are inherent to the surgical procedure(s) and the device
(3) Unwillingness or inability of the candidate to comply with all investigational requirements

[4] Pure Tone Audiometry can be performed within 6 months before the visit 2 (inclusion visit)
[5] Post-lingual deafness: occurs after the development of normal speech.

3.5 Study Procedures

For the complete timing of trial procedures, please refer to the scheduled activities in section 3.5.5.4.

Speech tests shall be obtained under reproducible conditions through a calibrated system (calibrated dedicated software). Tests shall be carried out by the same trained operators in a given participating center.

3.5.1 Screening Procedures

Prior to undergoing any trial procedures, subjects shall be required to provide a written informed consent form which has been approved by an EC/CA and which complies with regulatory requirements. Subjects shall be given the prior opportunity to sign this form, to ask the PI any questions about the trial, and to discuss the trial with a relative or other staff member. Subjects shall also be informed of alternative treatments and local approval.

To fulfill preoperative considerations, the following examinations must be conducted:

- Tympanometry[6] to ensure absence of middle ear diseases
- Imaging with CT or MRI to evaluate the inner ear and to ensure absence of auditory nerve lesions and/or cochlear malformation and/or more central lesions of the auditory pathway

3.5.2 Electrode arrays

The surgeon may elect to use one of two types of lateral-wall electrode arrays that are available for the Neuro Zti. The two electrode arrays are the Neuro ZtiCLA and the Neuro ZtiEVO. Both arrays have been extensively used OUS for several years on the prior generation implant and now in OUS implantations of the Neuro Zti. Both arrays provide 20 contacts, similar cochlear coverage and are amenable to round-window, modified round-window or cochleostomy insertions into the scala-tympani. To date, there is no evidence that speech perception outcome is impacted by the array choice and both of the array's dimensions are much smaller than the scala-tympani dimensions reported in the literature. Both arrays demonstrate stiffness profiles that fall within those demonstrated in existing designs by other manufacturers currently approved by the FDA. At present, the choice is left to the surgeon's preference. The principle difference between the arrays are that the "Classic" Array is slightly stiffer than the "EVO" making it slightly easier to achieve a full insertion. However, the less stiff EVO, is suspected to allow for a "softer" insertion which under certain conditions may result in a lower probability of cochlear trauma. To date, the EVO version is the most common electrode array used and the classic version tends to be used in cases of more difficult insertion due to anatomical issues or other issues that result in difficult insertion such as compromised patency of the scala-tympani due to fibrosis or ossification. Temporal bones studies have been conducted for both arrays and this data will also be provided in the PMA application.

3.5.3 Study Treatment or Diagnostic Product Procedures

Subjects are to be candidates for a cochlear implantation as assessed by tests and exams performed before surgery and are of clinical routine evaluation/use. The conventional surgical approach is described below. If an alternative surgical method or approach is used (e.g. suprameatal, cranial facial, or endomeatal approach), the subject should be excluded from the protocol and the investigator shall record this information in the CRF and document the rationale for the deviation in surgical approach.

[6] Tympanometry can be performed within 6 months before the visit 2 (inclusion visit).

The standard mastoidectomy-posterior tympanotomy introduced by House, 1961, is the gold standard for cochlear implantation, however some surgeons modified their approach to develop simplified and safer procedures, which is adaptable to possible situations such as anatomical anomalies or to have a shorter operative time and minimal morbidity with a possible decrease of facial nerve damage and chorda tympani sacrifice.

The Neuro CIS does not require special surgical techniques when compared to the CISs currently approved by the FDA and in Europe. The exception being that the Neuro Zti incorporates an integrated fixation system to prevent device migration.

The approach uses the facial recess is the well-known technique and used for many decades, other surgical technique used in this clinical trial will exclude the subject.

Surgical Procedure

The surgeon performing CI surgery, in this study, shall be experienced in otologic and neurotologic surgery. The surgeon shall also be experienced in cochlear implantation. The CI surgery is to be done under general anesthesia with a minimally invasive technique. The classical/conventional technique for cochlear implantation is to be performed for this study:

- A small postauricular incision shall be made and the temporal muscle and periosteum shall be elevated,
- The bone shall be exposed anteriorly to the level of the ear canal and posteriorly sufficient to accommodate the Neuro Zti's electronic housing.
- Mastoidectomy and posterior tympanotomy are to be performed with an extended facial recess approach.
- The tympanic membrane and the ear canal are not to be disturbed during the surgical procedure.
- For a round window (RW) insertion of the electrode, the posterior tympanotomy recess shall be drilled sufficiently to obtain a clear view of the round window (RW) and to obtain proper landmark identification to ensure electrode insertion into the scala-tympani. If warranted, the round-window niche should be reduced to expose the round window.
- A cochleostomy approach may also be considered, however, proper landmark identification and insertion vector shall be determined as standard for FDA approved CI systems to ensure scala tympani insertion.
- Prior to opening the cochlea, either the RW membrane for RW insertion or the endosteum for the cochleostomy, a drop of corticosteroid and/or hyaluronic acid may be placed on the RW membrane or endosteum to reduce fibrotic reaction.
- Once scala-tympani access to the cochlea is verified, the Neuro Zti shall then be placed in its position under the periosteum, posterior and superior to the ear and secured with the included self-tapping screws. Device positioning may be helped by use of included sterile surgical dummies of internal and external components.
- The RW membrane or endosteum shall then be incised and the tip of the electrode array shall be guided toward the cochlear opening. During insertion, no excessive force should be used (biocompatible lubricants may help smooth insertion).

- Following electrode insertion, the cochlea shall be sealed with a piece of fascia graft and/or bone wax, bone paté. The periosteum shall be sutured over the implant region and the mastoid cavity.
- The wound shall then be closed in layers with subcutaneous sutures and a suitable dressing shall be applied.
- For each implantation the surgeon shall be required to document the duration of the surgery (starting time i.e. skin incision, and ending time i.e. last skin flap suture).

After surgery, the rehabilitation procedures for study subjects shall be managed similar to FDA approved CI recipients (i.e. sound processor activation/fittings/mappings, speech therapy).

3.5.3.1 Allocation to Treatment

Not applicable.
Open label-trial.

A single identification number (SSID) is assigned at the inclusion visit that uniquely identifies each subject, it is composed of the site code and subject number |_|_|-|_|_|). The same CI system models shall be assigned for all subjects. The sound processor is available in different colors but the hardware and electronic features are identical between processors.

3.5.3.2 Breaking the Blind

Not Applicable

3.5.3.3 Treatment Adherence/Study Compliance

The importance of rehabilitation and study visit attendance shall be discussed with each subject.

The cochlear implant system must be used for at least 8 hours per day; system use will be verified via the subject diary. If a subject fails to utilize their cochlear implant system for at least 8 hours per day for more than 10 consecutive days and/or less than 85% of the total required wearing time for the study, the audiologist will ask the subject about the issue(s) and suggest alternatives.

This survey will provide useful information on subject complaints.

3.5.4 Withdrawal of Subjects Due to Non-Compliance

Subjects who are not compliant with study visits shall be withdrawn from the study. Subjects may withdraw from the trial at any time at their own request, or they may be withdrawn at any time at the discretion of the PI and/or the sponsor for safety, behavioral, psychological or administrative reasons. If the subject does not return for a scheduled visit, every effort shall be made to contact the subject. Regardless, every effort will be made to document subject outcome for all participants in the study.

For each subject that withdraws from the assessments detailed in the schedule of activities for visits, an “Early termination” shall be carried out. If the subject withdraws from the trial and also withdraws consent for disclosure of future information, no further evaluations will be performed and no additional data will be collected. The sponsor may retain and continue to use any data collected prior to the withdrawal of consent. Any withdrawn subject will be followed as a CI implanted patient and followed per regulatory guidelines.

Withdrawn subjects will not be replaced unless the total number of remaining subjects drops below 50 (10% loss). Should a subject withdraw or be withdrawn due to non-compliance, all available data regarding those that withdraw or are withdrawn will be provided and documented as a subgroup in a due-diligence effort to determine if a failure of the device to perform to specification was the reason or contributed to the reason of withdrawal or non-compliance.

The subject cannot participate in another study during this study. However, as there is no wash-out period at the end of this study, the subject can participate in another clinical trial at the end of this study.

3.5.5 Follow-up Procedures

An Oticon Medical Clinical Support could support the medical team in fittings and objective measurements. Roles and tasks are described in Appendix 6, the clinical support provides an assistance to the clinical team and should not interfere with subject clinical results.

3.5.5.1 Procedures to Assess Efficacy

For the timing assessments please refer to the schedule of activities in section 3.5.5.4.

Audiometric testing shall be performed by or under the direct supervision of an otolaryngologist, a qualified hearing aid acoustician/specialist, speech-pathologist, technician and/or by an audiologist qualified to perform such tests. The pivotal study should not disrupt the routine follow-up visits of each referral center (i.e. fittings, programming changes, speech therapy, audiology tests, and radiological control).

All subjects will use the same signal processing (e.g. directional microphone) and stimulation strategy (e.g. pulse shape, pulse rate).

All subjects, English and non-English speakers, will be assessed with the same procedure and setups
The Danish (20-sentences-list), the French Canadian (20-sentences-list) and the American English HINT (20-sentences-list) will be used according the local language.
The HINT tests will be conducted with dedicated HINT software.

a. Description

The HINT (Hearing in noise Test) was developed at the House Ear Institute (Los Angeles, California) and measures speech recognition thresholds in quiet and noise [3]. When used to determine implant candidacy, the HINT sentences are generally presented in quiet.

The HINT is recognized as a primary assessment instrument for measuring a subject's ability to hear in quiet and in noise. HINT was originally designed as an adaptive speech recognition test based on a correct response of the entire sentence [3]. An intensity level measurement for the sentence speech-reception threshold was determined by presenting random HINT sentences in competing speech-shaped noise (SSN). However, current clinical use of HINT sentences routinely deviates from this original design; instead, HINT sentences are presented in quiet to obtain an accuracy measure, which is important for determining cochlear implant candidacy [4]. Disability evaluation under social security, requires that this testing be conducted in quiet at 60dB SPL [10].

A digital recording is presented to the subject placed inside a sound isolation booth.

For this protocol, subjects shall be tested with two sentence lists

- during inclusion (visit 2)
  - in quiet and in noise in the best aided condition and
- at 3, 6 and 12 months (visits 6, 7 and 8 respectively)
  - in quiet and
  - in noise condition in the ipsilateral electrically stimulated ear with an occluded contralateral ear.

The noise and/or the signal shall be presented from the front of the recipient at 0° azimuth

b. Procedure

Speech perception tests will be conducted:

- Preoperatively, on both ear with the best fitted hearing aid(s), and
- Postoperatively, on ipsilateral ear with activated CIS and an occluded contralateral ear with ear-plug.

Ear-plugs will be supplied for all centers.

At visit 2 (preoperatively)

The test is conducted in quiet and in noise background, and in the best-aided conditions

In quiet:

The subject's is given practice sentences to become familiar with the task before each test. Then two 20-sentences lists of HINT shall be presented to the subject, in front (0° azimuth), in quiet at a conversational speech level of 60 dB SPL (Appendix 9: Calibration considerations). All words in the sentence repeated correctly, (Nilsson et al. 1994 [5]) shall be computed to calculate a score in percent correct of total words.

In noise:

As described above, the same procedure is applied for HINT-N, sentences are presented at +10dB SNR, with noise set at 55 dB SPL, and signal at 65 dB SPL.

From visits 6 to 8 (postoperatively)

The tests shall be measured in quiet and in noise. Measurements are performed in the ipsilateral ear with an occluded contralateral ear with ear-plug

In quiet and in noise, similar conditions of the test are used as described in visit 2.

Speech perception score are computed to calculate score in percent correct (%)

c. HINT score calculation in quiet and noise conditions

The ratio of words correctly repeated divided by the total of words for each list is multiplied by 100 to obtain the score in percent correct for the lists.

3.5.5.2 Procedures to Assess Safety

For the timing assessment please refer to the schedule of activities in section 3.5.5.4.

The PI shall be responsible for safety data collection.

The PI may plan any unscheduled consultations as needed to follow any adverse event.

All complications/adverse events are recorded and classified as major or minor complication by the investigator.

Serious Adverse Event or Major Complication (related or not related to the device) are those that are life-threatening (e.g. meningitis, death), those requiring hospitalization and/or resulting in disability or permanent damage (e.g. permanent facial nerve paresis, permanent chorda tympani syndrome, permanent vertigo/dizziness, persistent pain discomfort requiring device explant), those requiring revision surgery with or without re-implantation (e.g. device explant, surgery to prevent permanent impairment, large scalp necrosis, severe infection, electrode shifting, eardrum perforation, receiver positioning and cholesteatoma) and tinnitus, facial stimulation, pain that could not be alleviate by electrode deactivation; and other serious medical events.

Adverse Event or Minor Complication (related or not related to device) are those that resolve spontaneously without surgical intervention (e.g. wound infection treated by antibiotics; skin flap hematoma; transient or rising tinnitus; transient vertigo/dizziness; transient pain; transient chorda tympani syndrome; transient facial nerve palsy, and tinnitus, facial stimulation and pain that could be relieved by electrode deactivation), or with conservative medical management (medical complications, pre-existing conditions such otitis media).

All explanted devices returned to the manufacturer will be classified according the AAMI-CDV-4 CI86 guideline, and ditto for the non-implantable part (i.e. sound processor, accessories).

Description

All adverse events and serious adverse events related to surgical/medical procedures and/or device shall be collected from the time subject is implanted till the completion of the study and shall also include any unscheduled visits dealing with adverse events or serious adverse events.

Procedure for all complications

Any suspected adverse event should be recorded on the “Adverse Event Report Form”, and the serious adverse event on the “Serious Adverse Event Report Form” available directly in the ECRF.

For each adverse event, the outcome must specified at the end of the study.

Procedure for explanted device

Explanted device must be recorded on the “Explanted Device Report Form”
Every explanted device shall be tested to determine the reason for device failure, and device explantation shall be reported as a serious adverse event and classified according to AAMI-CDV-4 CI86 guideline.

All explanted devices shall be returned to Oticon Medical for a formal evaluation and a report shall be made according to the criteria specified in the AAMI-CDV-4 CI86 guideline. It will be the responsibility of the Oticon Medical Vigilance System to determine the final classification of the device failure. Concurrent with any reporting to Oticon Medical of an explant, a report shall also be sent to the Local Competent Authority having relevant jurisdiction.

Complications may lead to device explantation, in such cases initial SAE reporting shall specify the reason:

a. Explantation due to unrelated medical reasons, for example:
   Device is removed to enable diagnostic or therapeutic procedures for conditions unrelated to the implantation or function of the device (e.g. MRI scanning need outside manufacturer specification, radiotherapy, surgical resection, etc.)
b. Explantation for medical reasons associated with the device.
   Any device explanted with medical symptoms that could be related to the device and/or caused by device malfunction, for example:
   - Meningitis secondary to the cochlear implantation
   - Infection near the receiver/stimulator, lead and/or electrodes
   - CSF leakage due to the occurrence of CSF leakage secondary to cochlear implantation.
   - Skin flap complication secondary to the cochlear implantation
   - Allergic reaction to device components
   - Dizziness due to occurrence of balance and other vestibular-related issues
   - Pain or discomfort that cannot be eliminated with changes in program parameter settings (e.g. deactivating an electrode).
   - Tinnitus appearing during device use or an increase in pre-existing tinnitus
   - Extra-cochlear stimulation, stimulation at sites outside the cochlea (e.g. facial nerve, chorda tympani, or return electrode placement, etc.) secondary to cochlear implantation and resulting from medical related factors (e.g. anatomical malformation, otosclerosis, cochlea ossification, etc.)
   - Electrode array misplacement during cochlear implantation
   - Electrode migration out of the cochlea
   - Implant migration/extrusion
   - Performance issue, the patient experienced a performance decline and/or failed to achieve a clinically-expected performance level attributable to health-related issues
   - Change in patient behavior with the device use, such as refusing to wear the device
   - Other; a patient may experience a sign or symptom not listed above or due to an unforeseen medical reason.
c. Explantation because of suspected device failure.
   This category is determined by in-vivo testing which confirm malfunctions. For example:
   - Sudden loss of sound and/or gradual loss of function that occur over a short time
   - Loss of all connectivity with the implant
   - Shocking sensations, intermittent “popping” sounds, intermittent surges in loudness that exceed the loudness levels set by the clinician, and
   - Intermittent or permanent changes in speech perception or reported sound quality
   - Abnormal impedances accompanied by a change in sound quality
   - Performance decline because of a loss of functional electrode channels
   - Magnet issue/displacement
   - Case damage
   - Intermittent or unstable communication between internal and external components

Calculation

The proportion of patients experiencing a specified events shall be tallied and calculated.

Complications shall be classified as major and minor according to the Cohen & Hoffman criteria [23].

3.5.5.3 Procedure to assess technical functionalities

Impedance and ECAP measures will be performed per-operatively at the end of the surgery; at implant activation; at 3, 6 and 12 months post activation; and at unscheduled visit if available:

- Impedance helps to ensure the correct electrode/tissue contact, and the correct operation of the internal part. The test will takes 30 sec. or more if some electrodes impedance are out of range and need to be checked again.
- ECAP (Evoked Compound Action Potential) is the electrophysiological responses of the auditory nerve. The test will takes approximately 2 min (standard parameters: 4 electrodes stimulated, 6 measures and 50 repetitions per measures).

The impedance changes over time will be accessible from the patient maps in the fitting software. If any electrode turns out of range, it will be deactivated. Out of range electrode impedances can reflect degraded electrode-neuron interface, and can be related to electrical stimulation failure.
Calculation: average of each electrode impedance at different time points and description of localization and number of electrode failures.

The ECAP is the synchronous whole auditory nerve activity in response to an electrical stimulus. This is commonly measured by the difference in amplitude between two peaks (N1 and P2), characteristic from the human auditory nerve response [44]. These delays suffer from variations among both CI users and devices but is situated among 0.3 and 0.6 msec.
Calculation: average of N1-P2 amplitude at each time point.

3.5.5.4 Schedule of activities (Study Table)

Protocol activity	V1	V2	V3	V4	V5	V6	V7	V8	Unscheduled visit(s) #
	8 weeks pre-surgery	4 weeks pre-surgery	Baseline	2 weeks post-surgery	1 month post-surgery	3 months post-activation	6 months post-activation	12 months post-activation	
	Screening	Inclusion	Surgery	Follow-up	Activation	Follow up	Follow up	End of study	NA
	Week (-8)	Week (-4)	Week (0)	Week (+2) post-surgery	Month (+1) post-surgery	Month (+4) post-surgery	Month (+7) post-surgery	Month (+13) post-surgery	NA
Eligibility									
Informed consent	X*	X**							
Eligibility criteria		X							
Demographic data		X							
Medical and Hearing History		X							
Evaluations									
HINT-Q		X				X	X	X	
HINT-N		X				X	X	X	
Study device									
Surgery			X						
Implant activation					X				
Patient Diary									
Diary issued					X	X	X		
Diary returned						X	X	X	
Safety									
Adverse event reporting			X	X	X	X	X	X	X
Electrodes Impedance			X		X	X	X	X	(X)
ECAP			X		X	X	X	X	(X)
Concomitant medications		X	X	X	X	X	X	X	X

*Informed consent given

**Informed consent obtained

#unscheduled visits may occur in addition to the predefined protocol specific visits. Unscheduled consultations must be related to CI complications/adverse events and/or additional speech processor fittings. The PI may plan any unscheduled consultations as needed. Impedance and ECAP measurements are optional and depend on the nature of patient visit.

3.5.6 Permitted visit window periods

Visit	Visit interval (defined as number of weeks relative to visit 3, baseline)	Visit window (defined as number of days from previous visit indicated plus and/or minus day stated)	Visit window (defined as a range in days from previous visit indicated)
1	-8	NA	NA
2	-4	28 days from visit 1 (-25 to +14 days)	3-42 days from visit 1
3	0	28 days from visit 2 (+/- 14 days)	14-42 days from visit 2
4	+2	14 days from visit 3 (-7 to +6 days)	7-20 days from visit 3
5	+4	28 days from visit 3 (-3 to +6 days)	25-34 days from visit 3
6	+16	112 days from visit 3 (-7 to +6 days)	105-118 days from visit 3
7	+28	196 days from visit 3 (-7 to +6 days)	189-202 days from visit 3
8	+52	364 days from visit 3 (-7 to +6 days)	357-370 days from visit 3

3.5.7 Scheduled Visit Procedures

Visit 1 (screening, Week -8 pre-surgery)

Potential subjects shall be verified to be candidates for standard cochlear implantation, this screening process may be utilized to determine whether an individual may be appropriate for this study (e.g. motivation, geographical remoteness, willing to commit to protocol requirements, language skills).

Screening may be accomplished during a medical visit, telephone or telemedical consultation, by mail and/or through medical records. Prior to enrollment, all potential subjects shall be presented with the informed-consent form and shall be given the time to read, understand and/or request further information or clarification regarding study requirements and associated risks.
Consent is required once and may be obtained either at this visit or at visit 2.

Visit 2 (inclusion, Week -4 pre-surgery)

- Written informed consent: consent is required once and may be obtained either at this visit or at visit 1.
- Subjects will be assigned a single subject identifier (SSID) by the sponsor
- The physician and/or qualified clinician shall verify that the potential subject has appropriate hearing aid settings to be in the best aided condition in accordance with good clinical practice and audiological standards.
- Inclusion/exclusion criteria shall be reviewed to verify the potential subject meets all enrollment requirements
- Demography, medical history, concomitant medications and any potential contra-indications to study inclusion requirements shall be reviewed
- Audiometric evaluations: HINT-Q, HINT-N shall be obtained in the best-aided conditions
- Audiometric evaluations in routine care shall be recorded, if available
- Cochlear implantation scheduling shall be reviewed and confirmed

Visit 3 (implantation, Week 0 surgery)

Surgery shall be performed according to conventional cochlear implantation standards and good surgical clinical practice.

- Time of surgery and surgical approach shall be recorded on the CRF
- Objective measures: electrode impedances and ECAP if obtained, shall be recorded
- Complications/adverse effects shall be recorded
- Concomitant medication(s) shall be noted on the CRF

Visit 4 (follow-up, Week +2 post surgery)

- Perform clinical examination (general state, scarring, skin-flap assessment,)
- Complications/adverse effects shall be recorded
- Concomitant medication(s) shall be recorded

Visit 5 (activation, Month +1)

- Activation and fitting of Neuro CIS shall be performed
- Objective measures: electrode impedances shall be recorded
- Subject will be instructed in the use of Subject's diary
- Complications/adverse effects shall be recorded
- Concomitant medication(s) shall be recorded

Visit 6 (follow-up, Month +3 post-activation)
- Audiometric evaluations: HINT-Q, HINT-N scores shall be recorded
- Audiometric evaluations in routine care shall be recorded, if available
- Objective measures: electrode impedances and ECAP shall be recorded
- Review of returned Subject's diary
- Subject shall be reminded about the correct use of Subject's diary
- New Subject's diary dispensed
- Complications/adverse effects shall be recorded
- Concomitant medication(s) shall be recorded

Visit 7 (follow-up, Month +6 post-activation)
- Audiometric evaluations: HINT-Q, HINT-N scores shall be recorded
- Audiometric evaluations in routine care shall be recorded, if available
- Objective measures: electrode impedances and ECAP shall be recorded
- Review of returned Subject's diary
- Subject shall be reminded about the correct use of Subject's diary
- New Subject's diary dispensed
- Complications/adverse effects shall be recorded
- Concomitant medication(s) shall be recorded

Visit 8 (end of study, Month +12 post-activation)
- Audiometric evaluations: HINT-Q, HINT–N
- Audiometric evaluations in routine care shall be recorded, if available
- Objective measures: electrode impedances and ECAP shall be recorded
- Review of returned Subject's diary
- Complications/adverse effects shall be recorded
- Concomitant medication(s) shall be recorded

Unscheduled visit
- Visit purpose shall be recorded
- Objectives measures: electrode impedance and ECAP, if available
- Complications/adverse effects shall be recorded
- Concomitant medication(s) shall be recorded

3.6 Study Outcome Evaluations

3.6.1 Study Endpoints

3.6.1.1 Primary Endpoints

Previous studies analyzed their samples based on fixed time intervals after implantation, usually 1, 3 and 6 months, then annually thereafter. After 6 months of CI experience outcomes appear to be stable with the majority of users reaching a performance plateau. Massa et al. [5] observed a performance plateau at a median of 4.7 months post-implantation. Similar results were reported by Bradley et al. [8] demonstrated a plateaued performance around 6 months in a sample of 55 patients. In Dillon et al. study [9] the adults tested with HINT in quiet at 70 dB experienced growth in speech perception within the first 6 months and remained stable thereafter. This plateau at 6

months is generally consistent with findings from others previous research with other speech discrimination tools, as Lenarz et al. study [7] using German language tests in a large cohort.

a) HINT in Quiet (HINT-Q)

The primary efficacy endpoint of the Neuro CIS is assessed with the HINT score in quiet in the ipsilateral ear. The primary endpoint is the difference between the baseline performance in the best-aided condition and the performance in the implanted ear within 6 months following activation. The mean score of words correctly repeated in quiet will be used as the primary outcome measure for assessing the primary benefit.

b) Safety

The occurrence of major complications within the first year of follow-up will be the co-primary endpoint for assessing the primary risk of device implantation.

Safety data shall be collected through the duration of the study and reflect the type and duration of any adverse event(s) and classified as major or minor complications. Evaluations shall be performed from baseline, during the operative time, and at each time points.
Three estimations of incidence rate will be provided:

- Major complications rate (co-primary estimate of device side-effects)
- Minor complications rate (secondary evaluation of side-effects).
- Incidence rate of any complications.

It is expected that major complication incidence rate will be within the range of variation of estimations obtained in previous studies on old generations of devices. A forest plot will present the estimate and 95% CI of incidence rate for the investigational device and estimates and 95% CI obtained in previous studies and previous generations.

3.6.1.2 Secondary assessment criteria

a) HINT in quiet (HINT-Q) at month 3 and 12months

The secondary endpoint is the score of words correctly repeated in quiet determined at 3, and 12 months post-activation in the implanted ear and the performances compared overtime.

b) HINT in Noise (HINT-N)

This efficacy secondary criterion is the score of words correctly repeated in noise preoperatively and at 3, 6 and 12 months post-activation in the implanted ear and the performances compare overtime.

3.6.1.3 Other outcome of interest – Technical Functionalities

The average of electrodes impedance values are collected at the different time points and observed over time.
The average of N1-P2 peaks amplitudes are determined at each time point and observed over time.

3.6.1.4 Sample Size Determination

Sample size determination is based on the two co-primary endpoints: change from baseline to 6 months of the HINT-Q (efficacy assessment), and major complication incidence rate during the 12 month follow-up (safety assessment).

The expected efficacy is an improvement of 50 points at 6 months of device use.

Change from baseline to 6 months is not available in literature, but 2 studies describe the HINT-Q magnitude after 12 months of device use. Waltzman et al. [42] described an increase of 47.7% (SD=26.6%) from pre- to 3 months post-implantation, similar results are reported by Lin et al. [43] with a magnitude of 60% (SD=24.1%) at 12 months. Considering an observed performance plateau around 6 months [5,8,9,7], we can consider that standard deviation obtained at 3 and 12 months can be used for 6 months of device use in this study. In addition in the main studies conducted at 6 months [5,6,8,9], the standard deviation are ranged from 22% to 28%, which is consistent with results change from baseline. Data from literature using the same efficacy assessment criterion provided a weighted average ± weighted standard deviation change from baseline of 57.43% ± 25.05%.
Such estimation has been rounded conservatively to 50% ± 25%.

Sample size
The sample size required to have 95% chance to get a significant efficacy result assuming a true mean improvement of 50%, a standard deviation of change from baseline of 25% and a type I error of 0.025 (one-sided) is 7 patients. It means that the expected improvement is so large with respect to the variability that the sample size calculation is not driven by efficacy considerations.

As requested by the FDA, the sample size will be set at a total of at least 50 subjects to support the safety. If the incidence rate of major complications is 2% then the chance to observe at least one event is 63.5%. The exact upper limit of the 95% C.I. will be 10.6% for an observed rate of 2%. Regarding any complication the expected rate is 35%. If the observed rate is 36% then the precision is around 13% in points.

In order to ensure that at least 50 subjects will be implanted with the device, starting with the anesthesia followed by surgery procedure, 55 subjects will be included.

An arbitrary minimum of 39 English speaking patients and 16 non English speaking patients will be recruited to meet the FDA requirement. It is possible that the recruitment in a given language be smaller than expected. In this case patients from other languages may replace the shortage provided that a minimum of 5 French speaking patients and 5 Danish speaking patients be recruited to justify the class of language.

3.6.2 Outcome Data and Data Analysis

3.6.2.1 Analysis Set

a) Full Analysis Set (FAS)

This set will include all subjects implanted with the device, regardless whether any post-operative data are available. The primary analysis will be performed on a subgroup of this set. This subgroup is composed of English speaking patients to avoid the probable effect of language on the response.

b) Per-Protocol Set (PPS)

This set of patients is composed of participants who complete the clinical trial according to the protocol.
It consists of subjects who satisfy the following criteria:

- Complete the pivotal study
- Protocol compliance during the pivotal study (complete post-implantation visits)
- No violation of any eligibility criteria that could influence the primary efficacy endpoint
- No violation of the protocol or deviation from the protocol which could influence the outcome of efficacy endpoints.

The type of protocol violation and protocol deviations that are considered to influence the outcome of the safety endpoints will be defined in the statistical analysis plan.

The English speaking subgroup in the PPS will be used in a sensitivity analysis of the primary analysis.

c) Safety Analysis Set (SAS)

It consists of all subjects for whom surgery for implantation started.

3.6.2.2 Analysis of Efficacy Endpoint(s)

The primary analysis of the primary efficacy endpoint will be performed on a subgroup of the FAS which consists of all English speaking patients (Exclusion of Danish and French Canadian speaking patients). The primary test is a one sample T-test performed on the change from baseline to 6 months after activation of the device. The value of the mean improvement under the null hypothesis is zero. The type I error (α) is set to 0.025 (one-sided).

The one sample Wilcoxon rank test will be applied in a sensitivity analysis. In case the normality assumption is strongly violated or in the presence of several outliers the result of this sensitivity analysis will have a particular importance. The same analysis performed on the Per Protocol Set of patients in English speaking people will be another sensitivity analysis of the primary analysis.

3.6.2.3 Co-primary Analysis of Safety Endpoint

No formal hypothesis testing of safety data will be performed. The safety analysis consists of all enrolled subjects for whom implantation surgery was initiated. The incidence rate of major complications will be presented as well as its 95% exact confidence interval. A forest plot will present this rate with its 95% C.I. and the rates with the 95% C.I. of major complications in studies carried out with older generations of cochlear implants.

3.6.2.4 Secondary analyses

Claims for labeling will be based only on confirmatory results demonstrate through the primary analysis.

All secondary or sensitivity analyses are supportive estimates of effects related to the primary or secondary objectives.

a) Time course of the HINT-Q response in the primary population

The time course of the change from baseline in the HINT-Q will be estimated with a mixed model for repeated measures using the change from baseline as the response, the patients (random effect) and the visit (fixed effect) as covariates. The analysis will be done on the FAS subset of English speaking patients.

The time (visit) effect will be tested (H1: at least two visits differs on average) and if a significant effect of visits is observed then visits responsible for the significant difference will be searched. The 95% confidence interval of the mean at each visit will be provided.

b) Sustainability of the effect at month 12

HINT in quiet conditions performed at month 6 in English speakers will be compared to the result at month 12 to assess the sustainability of the effect over time. A one-sided (α = 0.025) t-test for paired samples will be used for that purpose.

c) Difference in the time course of HINT-Q responses across languages

The FAS including all patients instead of the subset of English speaking patients will be used in these secondary analyses. A mixed model for repeated measures will be fitted using the change from baseline to M3, M6 and M12 in the HINT-Q score as the responses and the following covariates or terms: the visit (M3, M6 and M12, fixed effect), the patient (random effect), the language (fixed effect) and the interaction between visit and language. The variance covariance matrix will be unstructured. If the p value of the interaction is below 0.15 then a signal of potential interaction is detected and the time course of speech performance is possibly dependent upon the language. Regardless the p value of interaction a graph will present the time course of the response for each language.

A series of contrasts will be performed to estimate and test:

1) The difference between languages in the change from baseline at each time point.

The estimate and test at M6 will be the most supportive result.

2) The overall mean change from baseline at each time point. The test against no change will be performed. Results will be easily interpreted in the absence of potential interaction (No significant difference in the time course of response between the 3 languages.

3) The overall difference between M6 and M12 in the change from baseline to assess the sustainability of effect in the overall population. This estimate is interpretable in the absence of interaction between visit and language. In the presence of interaction the difference is not easily interpretable and sustainability will be estimated and tested in the English speaking patients only.

d) Analysis of HINT-N

All analyses performed on the HINT-Q will be performed on the HINT-N, the response will be the change from baseline.

e) Measures of impedance

The time course of electrodes impedance performed at each time points will be analyzed through a mixed model for repeated measure and contrasts of interest will be described in the SAP.

f) ECAP

ECAP measures amplitude between (N1-P2) peaks. Measures will be performed over time from baseline to 12 months. The times course of the response will be fitted to a mixed model for repeated measures and contrast of interest will be describes in the SAP.

g) Safety analysis

The incidence rates of 1) minor complications, 2) any complications and 3) any adverse events will be estimated with their 95% C.I. in the safety population. The time to the first minor or major complications will be investigated through Kaplan Meier survival (event free) analysis and the graph of the estimated event free probability by the time will be presented.

A breakdown of all adverse events by categories will be done. The occurrence rates and 95% CI within each category will represent the safety profile of the new device. The observed rate in previous generations of device will be provided as a yard stick if they are available. Results from safety assessments will be presented in a tabular and/or graphical format (Forest plot).

Data regarding the average surgical time will also be reported.

h) Handling of site effects

The site effect is partly confounded with the language effect. Consequently the site effect will be investigated in English speaking patients. An analysis of variance using the change from baseline to M6 as the response and the site as covariate will be performed. If the site effect is significant, then the mean change from baseline to M6 is dependent upon the site. Regardless the p value of ANOVA a Forest plot presenting the mean change from baseline to M6 of each site along with the 95% confidence interval will be presented to verify whether there is just a quantitative difference across sites or a qualitative one. In case of significant site effect and qualitative difference the site with the largest mean deviation from the overall mean change from baseline will be removed from the sample to estimate the overall mean change from baseline in the remaining sites.

3.6.3 Handling of Missing Data

3.6.3.1 Imputation rules used in the primary analysis

Rule 1: If the assessment at M6 is missing but a further assessment is available the missing assessment will be replaced by the next available data.
Rule 2: If the assessment at M6 and M12 is missing but the assessment at M3 is available then M3 score will be carried forward.
Rule 3: If the assessment at M6 and M12 is not available in quiet conditions but available in noise then the score at M6 in noise will be used.
Rule 4: In case of lost to follow-up or withdrawal of the inform consent for unknown reason a stochastic regression imputation will be used.
Rule 5: In case of withdrawal not due to a failure of the implantation or complications the baseline will be imputed at month 6.
Rule 6: In case of withdrawal due to major complications requiring new implantation the worst score (0%) will be imputed.

3.6.3.2 Sensitivity analyses

- The best case scenario will consist in deleting patients without data at M6 and M12 (if M12 is available then M12 will be imputed at M6).
- The worst case scenario will consist in imputing a total loss of hearing (score = 0%)
- Tipping point analysis approach will be applied to assess the rules which overturn the conclusion. The steps going from the best scenario to the worst one (all missing scores are 0) and including rules of the primary analysis as intermediary step will be described in the SAP.

3.6.4 Futility/Safety Interim Analysis

Interim analyses will be performed on the safety endpoint. This is based on real-time information given by the monitoring and ECRF.

The trial could be stopped prematurely if the cumulated number of major complications is beyond the worst case scenario reported in the literature. Indeed, literature data reported a weighted average of 7.1±2.0% major complication rate over many years of experience [16,17,18,19,20,21]. Consequently if the number of observed major complication as described in section 3.5.5.2 is beyond (7.1%+2%)*55= 5 cases the study should be stopped prematurely for safety reason.

Actually at the 5th major complications during the inclusion period, the DSMB will meet expressly to decide how to move forward on the benefit-risk balance change (e.g. protocol amendment, temporary halt or early termination).

Once the inclusion period is over, the study will go to the end and the complications gather in the safety final report.

3.6.5 Data and Safety Monitoring Board

Each SAE will be submitted to the DSMB.
If more than 4 major complications are reached during the inclusion period, an extraordinary meeting of the DSMB will take place within the 7 calendar days.
The DSMB shall be notified each time an SAE occurs. Monitoring of key safety endpoints will be conducted as described above, and if rates significantly exceed pre-set thresholds, Competent Authorities will be notified and information supplied to the DSMB.
DSMB's Policies are described in the Oticon Medical Manual Procedures (composition/organization).
The data safety monitoring plan, describe:

- Type of data or events captured under the monitoring plan
- Names of persons who will be responsible for monitoring the data collected
- The frequency of assessments/analysis of data or events captured by the monitoring plan (e.g. periodic time interval, or after a specific number of participants are enrolled)
- Time frame for reporting unanticipated issues, adverse effects, protocol deviations, protocol violations
- Definition of specific events or stopping rules dictating when some actions are required
- Procedure and timeframes for communication outcomes of monitoring reviews to investigator sites, EC and CAs.
- Plans to monitor adherence to the EC/CA-approved protocol and assure the validity and integrity of data.

The DSMB should also assess the performance of overall operation study.

3.6.6 Early Stopping Rules

No statistical stopping rule for success is applied for the primary efficacy endpoint.

If no interim analysis shows safety endpoint values greater than the pre-set limit, the study shall continue until completion (Please refer to section 3.6.4).

3.6.7 Study Interruption or Withdrawal

Premature termination of this clinical trial may occur because of regulatory authority decision, change in opinion of the EC/CA, safety problems, or at the discretion of Oticon Medical. In addition, Oticon Medical retains the right to discontinue the trial at any time.

If a trial is prematurely terminated or discontinued, Oticon Medical will promptly notify the PI. After notification, the PI must contact all participating subjects within 24 hours. As directed by Oticon Medical, all trial materials must be collected and all CRFs completed to the greatest extent possible.

4. RISK ANALYSIS

4.1 Expected clinical benefits

The Neuro CIS has many similar features to the previous CIS (Digisonic SP + Saphyr SP Neo) and incorporate some of the same technologies. The two principle new features implemented into the Neuro Zti implant are the removable magnet and the ECAP recording hardware. These 2 features are currently incorporated into FDA approved CISs. The new features implemented in the Neuro One processor are related to hearing aid technology integration for signal processing (integration of directional microphones, etc.), but coding strategy and stimulation principles are similar between the Neuro CIS and the Digisonic CIS.

Expected clinical benefits are comparable to other CIS systems available on the market: for example Bergeron et al. [28] compared devices with the most recent technologies using HINT tests and showed an improvement of Digisonic SP + Saphyr Neo CIS compared to competitors in quiet and some noisy conditions (+10dB SNR), and similar performance in other noisy conditions among all devices..

4.2 Anticipated Adverse Events

Risks of general anesthesia

- ***General anesthesia***. Individuals may react differently to anesthesia. Although the risk associated with general anesthesia to obtain a cochlear implant is outweighed by the potential benefit for most candidates, individuals with certain medical conditions may be at higher risk for complications.

Risks of cochlear implant surgery

- ***Injury to the facial nerve***. The facial nerve traverses through an anatomical region near the cochlea to provide movement to the muscles of the face. The nerve lies close to where the surgeon needs to place the implant and may be injured during surgery. An injury to the nerve may cause a temporary or permanent weakening or even full paralysis on the same side of the individual face as the implant.
- ***Meningitis***. This condition results from an infection that results in inflammation of the meninges that line the central nervous system. Meningitis may result in serious complications including permanent brain damage or death. Individuals who experience inner ear structure anomalies or malformations and/or are implanted with a cochlear implant may be at an increased risk of meningitis.
- ***Cerebrospinal fluid leakage***. The brain and central nervous system are surrounded by fluid that may leak from a hole created in the inner ear during surgery. An uncontrolled leak of CSF may result in serious injury or death.
- ***Perilymph fluid leakage***. The inner ear contains a fluid called perilymph. This fluid, which is continuous with CSF, may leak through a hole created for electrode array placement.
- ***Infection*** of the wound or the implant. This includes the risk of otitis media which may cause infection on the implant either outside the cochlea or within the ear. In the case of infection that cannot be resolved with antibiotics, the device may need to be explanted to resolve the infection.
- ***Skin flap issues***. Although this will typically resolve with treatment, in the worst case the device may need to be explanted, with re-implantation once the infection has resolved.
- ***Cholesteatoma*** formation.

- ***Blood or fluid collection/edema*** at the site of the surgery
- ***Vertigo or dizziness***
- ***Tinnitus***
- ***Taste disturbance***. The sensory nerve that conveys taste sensations from the tongue also passes through the middle ear and may be injured during the surgical procedure.
- ***Stiffness or Numbness*** in the area around the surgical site
- ***Reparative granuloma***. Is the result of localized inflammation and may occur if the body rejects the implant.
- ***Pain***.
- Unforeseen complications due to the surgical procedure
- Unforeseen complications that could occur with long term implantation that cannot be predicted beforehand

Risk associated with the device

A study participant:

- May have skin irritation or redness behind the ear. Removal of the sound processor is recommended until the issue is resolved.
- May have skin irritation or redness in and around the implanted area. A magnet holds the antenna in place against the skin on the implanted device. Reduction in the magnet strength is recommended.
- May have to undergo device explanation if an infection occurs after the implant surgery that cannot be resolved with antibiotics. This is a rare complication.
- May have the sensation of heat or burning due to an increase in the processor temperature. The individual may remove his/her processor immediately.
- May experience an uncomfortably loud sensation. The T and C level thresholds are based on each individual's responses during the fitting session.
- May remove the processor before medical examinations and treatments; radiotherapy, MRI, ultrasound, scan, treatment using electric currents.
- May be able to undergo some medical examinations and treatments with caution and under specified conditions:
    - MRI imaging at 3 Tesla may be obtained with implant magnet removal. A minor surgery is required to remove the magnet beforehand. The implant is 1.5T compatible, however, if the medical region of interest falls within the projected artifact produced by the implant, the magnet may be removed to minimize artifacts.
    - Neurostimulation, when not directly over the implant.
    - Electrical surgery. Monopolar electrosurgical instruments may not be used on the head or neck area during and following implant placement.
    - Ionic radiation therapy.
    - Electrotherapy may be not used on the head and neck area.
    - Diathermy may be not used on the head and neck area.
    - Defibrillation may cause device damage but may be used in life-threatening situations.
- May be not able to have electroconvulsive therapy.
- May lose residual hearing. The implant may damage any remaining hearing in the implanted ear.

- May be at risk for dislocation and/or migration and/or demagnetization of the implanted magnet through a strong magnet field, or other conditions such as exposure to an MRI scan. Such conditions may require revision surgery to replace the magnet.
- May be at risk for electrode array misplacement. This is a rare and correctable complication that may require revision surgery to re-insert and secure the electrode. To further mitigate this risk, final electrode position is confirmed by visual inspection prior to closing and inferred by impedance and ECAP measures at the end of surgery.
- May exhibit device rejection which may result in the extrusion of the implanted components and/or necessitating the need for device removal.
- May be at risk for the electrode array being damaged during surgery.
- May be at risk for electrode post-surgical electrode migration requiring revision surgery to re-insert and secure the electrode.
- May experience an internal device failure. The individual would need to undergo additional surgery to resolve this issue and be exposed to additional surgical risk.
- May develop the need to have the CIS removed for medical reasons.
- May be at risk for impact or trauma near the implanted components resulting in partial or complete failure of the implanted components. Accidents, slips, trips, falls, contact sports, and any external impact may increase the risk of damage to the implant. Device failure would require revision surgery for correction.

Other risks associated with the use of the cochlear implant

A study participant:

- May hear sounds differently. Those who could hear before they became deaf report that cochlear implants may not sound like “natural” hearing. At first, it is not uncommon for users to describe the sound as “mechanical”, “technical” or “synthetic”. This perception changes over time and most users do not notice this artificial sound quality after a few weeks of CI use.
- May not hear as well as others who have had successful outcomes with their CI.
- May not be able to understand spoken language well. There is no test an individual can take before the surgery that predict how he/she will understand language after surgery.
- May have an altered perception of sound. They may require numerous changes to program settings to achieve the best sound quality.
- May have to use another processor than their own.
- May fail to use the device properly. User action may be limited by the audiologist with only one standard mode program.
- Will depend on batteries for hearing. Autonomy of batteries may be less than a working day.
- May receive intermittent, reduced and/or absence of sound. The individual should check his/her processor status; correct connection of the antenna cable, quality of the microphone using the earphones and battery life.
- Will have to take precautions to avoid electrostatic discharge. Static electricity may temporarily or permanently damage the CI. To prevent this issue, it may be good practice to remove the processor before contact with static generating materials such as TV screens, plastic equipment, or synthetic fabric, or to remove any residual static electricity by touching the individual wearing the CI prior to touching the processor.
- May have to undergo lifestyle changes if their CI interacts with the electronic environment (e.g. the device may set-off theft detection systems, set-off metal detectors or other

security systems, it may be requested that the device be turned off during take-off and landing in an aircraft, and the device may interact in unpredictable ways with other electronic systems).
- May hear strange sounds or experience interference resulting from device interaction with other electro-magnetic fields.
- May have unknown and/or other certain effects. The CI stimulates the nerve directly with electrical currents. Although this stimulation appears to be safe, the long term effect of these electrical currents on the nerve is unknown.

Performance decline may be related to different causes including but not limited to the following:
- Abnormal sound perception:
  - Unusual sounds when thresholds are low
  - Loud bursts of sound percepts
  - Sound popping
  - Other unusual sound perception
- Pain
  - Pain over the implant
  - Pain under the processor hook (the hook can be replaced or its shape adapted).
- Documented performance decrement
  - Sudden loss of auditory ability
  - Decrement of hearing ability over time or lack of expected progress according to speech perception measures
  - Intermittent auditory function
  - Failure to meet predicted performance level
  - Reduction in or lack of meaningful speech understanding
  - Lack of sound clarity
  - Loss of electrodes over time
  - Implant magnet issues
  - Regression in language understanding and speech production
  - Deterioration in school or work performance
  - Other performance decline
- Medical issues
  - Infection
  - Meningitis
  - Wound issues
  - Vertigo, dizziness
  - Headaches
  - Cholesteatoma
  - Facial nerve stimulation while the implant is on
  - Other medical issues
- Behavioral issues
  - Unwilling to wear the device
  - Being frequently “off line”- failure to use the device as prescribed
  - Other behavioral issues
- Other observations.

4.3 Trial Anticipated Risks

Subjects participating in this pivotal study shall be candidates for cochlear implantation, the risks are related to the surgery, no additional risks are provided by the trial compared to FDA approved cochlear implant designs. Audiometric tests (HINT) used in the trial are standardized and routine clinical tests. The 60 dB SPL signal presentation level is the average of conversational speech used for HINT-Q. HINT-N follows a routine standardized procedure. The study visits are closely matched to a cochlear implant recipients' routine visits to limit additional subject travel.
Subjects who agree to participate will have the same expectation of benefit as a routine cochlear implant recipient.

4.4 Benefit-risk Ratio

According to the risk analysis of the Neuro One and Neuro Zti, the majority of risks have limited severity; any risk to external components may be managed by removing and/or replacing the externals. Major risks are related to the implantable part, related to surgical/medical complications and device-related failure and they have a limited probability of occurrence as well as limited severity. Moreover, cochlear implantation is a therapy now used for more than 25 years, ENT knowledge and training is well developed today ensuring limited medical side-effects and effective patient care and follow-up.

The Neuro CIS is indicated for patients suffering from severe to profound hearing loss with limited benefit from appropriately fitted hearing aids. Therefore, these patients have no other alternative than cochlear implantation to enable the possibility of improved auditory function. Expected auditory benefits enable cochlear implant users to understand speech even in noisy situations. Cochlear implantation has been well documented to enable restored communication ability and social interactions for adults.

In light of the expected benefit of this product compliant with the essential requirements, and the identified risks, the risk-benefit balance is favorable.

4.5 Adverse Event Recording/Reporting

4.5.1 Adverse Events

All observed or volunteered adverse events regardless of investigational device or suspected causal relationship to the investigational device shall be reported as described in the following sections.

For all adverse events, the investigator shall pursue and obtain adequate information both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as serious adverse events (see section 4.5.6) requiring immediate notification of Oticon Medical or its designated representative. For all adverse events, sufficient information shall be obtained by the investigator to determine the causality of the adverse event. The investigator shall be required to assess causality. For adverse events with a causal relationship to the investigational device, follow-up by the investigator shall be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator and Oticon Medical concurs with that assessment.

4.5.2 Reporting Period

Serious adverse events require immediate notification of Oticon Medical or its designated representative beginning from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the clinical trial, i.e. prior to undergoing any trial related procedure and/or receiving investigational device, up to and including 28 calendar days after last visit. Any serious adverse event occurring any time after the reporting period must be promptly reported if a causal relationship to the investigational device is suspected.

Adverse events (serious and non-serious) should be recorded on the CRF from the time the subject has been implanted through 28 calendar days following the last subject visit.

4.5.3 Definition of Adverse Event (AE) and Adverse Device Effect (ADE)

An AE/ADE is any adverse change from the subject's baseline condition, i.e. any unfavorable and unintended sign including abnormal laboratory findings, symptoms or disease which is considered to be clinically relevant by the investigator that occurs whether or not it is considered to be related to the medical device.

AE/ADE include:

- Exacerbation of a pre-existing disease.
- Increase in frequency or intensity of a pre-existing episodic disease or medical condition.
- Disease or medical condition detected or diagnosed after treatment with the medical device even though it may have been present prior to the start of the clinical investigation.
- Continuous persistent disease or symptoms present at baseline that worsen following the start of the clinical investigation.
- Lack of efficacy in the acute treatment of a life-threatening disease.
- Events considered by the investigator to be related to clinical investigation-mandated procedures.
- Abnormal assessments, e.g., ECG and physical examination findings, must be reported as AEs/ADEs if they represent a clinically significant finding that was not present at baseline or worsened during the course of the clinical investigation.
- Laboratory test abnormalities must be reported as AEs/ADEs if they represent a clinically significant finding, symptomatic or not, which was not present at baseline or worsened during the course of the clinical investigation leading to interruption or permanent discontinuation of medical device.

AE/ADE do not include:

- Pre-planned interventions or occurrence of endpoints specified in the CIP that are not considered AEs/ADEs, if not defined otherwise.
- Medical or surgical procedures, e.g. surgery, endoscopy, tooth extraction, transfusion. However, the event leading to the procedure is an AE. If this event is serious, the procedure must be described in the SAE/SADE narrative.
- Pre-existing disease or medical condition that does not worsen.
- Situations in which an adverse change did not occur, e.g., hospitalizations for cosmetic elective surgery or for social and/or convenience reasons.
- Misuse of either medical device or concomitant medication without any signs or symptoms. However, misuse must be mentioned in the Medical Device Inventory/ Treatment Log.

An Adverse effect is defined as any untoward medical occurrence in a subject following device implantation or device use.

An AE does not need to be a causal relationship between the effect and the investigational device procedure or device usage.

AEs include, but are not limited to:
- Abnormal test findings
- Clinically significant symptoms and signs
- Changes in physical examination findings
- Progression/worsening of underlying disease

All AE are reported on the Adverse Event Form (Appendix 3).

4.5.4 Abnormal Test/Exam Findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:
- Test result is associated with accompanying symptoms and/or,
- Test result requires additional diagnostic testing or medical/surgical intervention and/or,
- Test result leads to a change in trial procedure or discontinuation from the trial, significant additional concomitant treatment, or other therapy, and/or
- Test result is considered an adverse effect by the investigator or the sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

4.5.5 Adverse Device Effect Definition

Adverse event related to the use of the investigational medical device.
This includes any adverse event resulting from insufficiencies or inadequacies in the instruction for use, the implantation surgery or any malfunction of the investigational medical device.
This includes any event that is a result of a use error or intentional misuse.

4.5.6 Serious Adverse Event definition

A Serious Adverse Event or Serious Adverse effect is defined as any untoward medical occurrence that:
- Results in death,
- Is life-threatening illness or injury,
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability/incapacity, or
- Is considered an important medical event

Life-threatening adverse effect. Any adverse effect that places the subject, in the view of the PI-sponsor, at immediate risk of death from the effect as it occurred (i.e., does not include an adverse effect that, had it actually occurred in a more severe form, might have caused death).

Hospitalization shall include any initial admission (even if less than 24 hours) to a healthcare facility as a result of a precipitating clinical adverse effect; to include transfer within the hospital to an

intensive care unit. Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse effect (e.g., for a preexisting condition not associated with a new adverse effect or with a worsening of the preexisting condition; admission for a protocol-specified procedure) is not, in itself, a serious adverse effect.

Disability. A substantial disruption of a person's ability to conduct normal life functions.

Important medical events include experiences that may not result in outcomes meeting the seriousness criteria, but that are still considered SAEs and should be reported as such. An important medical event may not result in death, be life-threatening, or require hospitalization, but would still be considered a SAE when, based on appropriate medical judgment, it

- May jeopardize the subject
  and/or
- May require medical or surgical intervention to prevent one of the outcomes listed in the SAE definition (e.g. death, life-threatening, hospitalization).

Serious Adverse Event includes device deficiencies that might have led to a serious adverse event if a suitable action had not been taken or intervention had not been made or if circumstances had been less fortunate. These are handled under the SAE reporting system.

4.5.7 Serious Adverse Device Effect

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

4.5.8 Unanticipated Serious Adverse Device Effect

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

4.5.9 Eliciting Adverse Effect Information

Subjects shall be routinely questioned about adverse effects at study visits. Subject may also change from one interval or may require unscheduled visits due to changes in subject circumstances, for example a subject may be admitted to a health care institution for an issue that may or may not be study related after which a study visit is required to determine the impact on the study participation, the adverse effects nature/cause.

4.5.10 Recording and Assessment of Adverse Effects

All observed or volunteered adverse effects (serious or non-serious) and abnormal test/exam findings, or suspected causal relationship to the investigational device shall be recorded in the subjects' case histories. For all adverse effects, sufficient information shall be pursued and/or obtained so as to permit:

- An adequate determination of the outcome of the effect (i.e., whether the effect should be classified as a serious adverse effect) and;
- An assessment of the casual relationship between the adverse effect and the investigational device

Adverse effects or abnormal test findings felt to be associated with the investigational device shall be followed until the effect (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the PI.

Unscheduled visits will allow for additional safety data collection.

4.5.11 Causality and severity assessment

The PI will promptly review documented adverse effects and abnormal test findings to determine:

- If the abnormal test/exam finding should be classified as an adverse effect;
- If there is a reasonable possibility that the adverse effect was caused by the investigational device; and
- If the adverse effect meets the criteria for a serious adverse effect.

Assessment and monitoring of adverse events are required to be classified as to the severity and relatedness to the study intervention.

Severity

"Severe" does not necessarily mean "Serious".

On the CRF, 3 categories of severity are defined for an AE:

- Mild: does not interfere with subject's usual function.
- Moderate: interferes to some extent with the subject's usual function.
- Severe: interferes significantly with subject's usual function.

Relatedness

Causality assessment involves determination of whether there is a reasonable possibility that the investigational device (or clinical study procedure) caused or contributes to an AE.

The causality of each AE must be assessed and reported in the CRF. In the case of SAEs, this same assessment shall also be recorded on the SAE Reports Form (Appendix 4). This report form shall include a description of the SAE in sufficient detail to allow for:

- Complete medical assessment
  and
- Independent determination of possible causality

The potential event relationship to the study intervention and/or participation is assessed by the site investigator. A comprehensive scale in common use to categorize an event is:

- Definitely Related: The adverse event is clearly related to the investigational device/procedure – i.e. an event that follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, that is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the subject's clinical state.
- Possibly Related: An adverse event that follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, but that could readily have been produced by a number of other factors.
- Not Related: The adverse event is clearly not related to the investigational device/procedure. - i.e. another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the study intervention and/or a causal relationship is considered biologically implausible.

4.5.12 Reporting Requirements

Each adverse event is to be assessed to determine if it meets the criteria for serious adverse event. If a serious adverse event occurs, expedited reporting will follow local and international regulations, as appropriate.

All adverse events shall be reported on the adverse event form of the CRF. It should be noted that the form for collection of serious adverse event information is not the same as the adverse event CRF. Where the same data are collected, the forms shall be completed in a consistent manner. For example, the same adverse event term should be used on both forms. Adverse events should be reported using concise medical terminology on the CRFs as well as on the form for collection of serious adverse event information.

Explantation and revision surgery shall be reported completely and separately on specific forms.

4.5.13 Serious Adverse Event Reporting Requirements

If serious adverse event occurs, Oticon Medical shall be notified within 24 hours of awareness of the event by the investigator. In particular, if the serious adverse event is fatal or life-threatening, notification to Oticon Medical shall be made immediately, irrespective of the extent of available adverse event information. This timeframe also applies to additional new information (follow-up) on previously forwarded serious adverse event reports.

In the rare event that the investigator does not become aware of the occurrence of a serious adverse event immediately, the investigator shall report the event within 24 hours after learning of it and document the time of his/her first awareness of the adverse event.

For all serious adverse events, the investigator is obligated to pursue and provide information to Oticon Medical in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Oticon Medical to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured for the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of causality. Information regarding other possible causes of the event, such as concomitant medication and illness must be provided. In case of a subject death, a summary of available autopsy findings shall be submitted as soon as possible to Oticon Medical or its designated representative.

Contact:
Oticon Medical Neurelec
M. Dan GNANSIA
Mobile: +33 4 93 95 18 18
Fax: +33 4 93 95 38 01
Mail: DAGN@oticonmedical.com

4.5.14 Non-serious Adverse Event Reporting Requirements

Non-serious adverse events are to be reported on the adverse event CRFs, which are to be submitted to Oticon Medical.

4.5.15 Reporting of Serious Adverse Effects to EC/CA

Serious adverse effects are reported by the Sponsor to the EC and/or CA.

Fatal or life-threatening adverse events shall be reported to the Competent Authority of the Concern member state and reported to the Ethical Committee within 7-days. A follow-up report shall be submitted within an additional 8-days. Other Unanticipated serious adverse events shall be reported to the CA of the concerned Member state as well as to the EC within 15-days.

4.6 Withdrawal of a Subject Due to Adverse Effect(s)

Withdrawal due to adverse effect(s) shall be distinguished from withdrawal due to insufficient efficacy, according to the definition of adverse effect noted earlier and recorded on the appropriate adverse event CRF.

If a subject withdraws due to a serious adverse effect, the serious adverse event shall be reported in accordance with the reporting requirements defined in section 4.5.

5. DESCRIPTION OF THE INVESTIGATIONAL DEVICE

The Neuro CIS is described in detail in Appendix 1. The principle mechanism of action involves detecting acoustic information with an external microphone, processing this information with the external sound processor and using the implanted components to directly stimulate the auditory nerve with electrical pulses.

The Neuro CIS is composed of an implanted part (named “Neuro Zti”) and an external part (named “Neuro One”). The Neuro One detects and processes sound and is designed to be worn behind the ear (BTE). The Neuro Zti is designed to be surgically implanted and consists of the receiver/stimulator which is implanted under the skin on the temporal aspect of the skull and a multichannel electrode designed to be placed within the Scala Tympani of the cochlea enabling electrical stimulation of the auditory nerve. All power and data are transmitted from the Neuro One to the Neuro Zti via an inductively coupled transcutaneous link. A complete system description is provided in Appendix 1.

6. MONITORING PROCEDURES

Monitoring is accomplished by the quality control activity.
Responsibilities include overseeing the progress of a clinical study and ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs, Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

The Sponsor or its representative shall be responsible for conducting study monitoring. The Sponsor or its representative shall appoint an appropriately qualified person(s) to monitor the trial. The monitor(s) shall be trained regarding the study protocol and shall be familiar with all study procedures.

Monitoring will focus on the following key processes of the study to ensure the protection of rights and well-being of all study participants and the integrity of data:

- Informed consent process
- Study eligibility criteria met for all participants
- Timely completion of Study CRFs
- Review of data management procedure i.e. data entry, handling of data discrepancies and data backup
- Reporting of adverse events and protocol violations according to Sponsor or its representative SOP(s)
- Follow up assessments and procedures

For each visit on site, the monitor shall work according to an agreed schedule of tasks, including the following that shall be given as specifics in the monitoring form and guidelines:

- Schedule a date with the study investigator/coordinator for the monitoring procedure and provide them with a list or outline of the study sections that will be monitored in this particular visit.
- Review last monitoring procedure report.
- Review the Site Study File: ensuring that it is updated appropriately.
- Verify that written informed consent was given by every subject entered into the study and obtained according to the consent sponsor or its representative SOP.
- Review current status of the study's participant enrolment vs. anticipated enrolment, losses to follow up, outstanding data issues and reported serious adverse events.
- Review the study forms and database ensuring that the participants were eligible and note any safety issues and protocol violations or deviations.
- Source data verification - abstraction of data from clinical and laboratory forms.

During the initial visits, the monitors shall review 100% of the fields of all the study forms. Subsequently the monitors shall review 100% of the data contributing to the primary endpoint and 100% of fields for a randomly selected sample of study forms. All forms monitored during a visit shall be detailed in the monitoring visit report. A database check for accuracy of data entry shall be performed at regular intervals. The data points to be checked will be safety data endpoints.

The investigator shall permit direct access of medical records and source data to the sponsor or its representative and appropriate regulatory authorities to verify the accuracy of this data.

After each monitoring visit the monitor shall debrief the study team i.e. reinforce aspects where they are meeting expectations and highlight areas which need improvement. The monitor shall then create a monitoring report citing all findings and status of such findings (resolved or not) and forward a signed copy to the sponsor and/or sponsor appointed project manager. The monitoring report may be shared with the PI.

At close out visit(s) the monitor will ensure all queries are resolved; the study product is accounted for and returned or destroyed according to sponsor or its representative SOP; and study documents are properly archived.

6.1 Study Monitoring Plan

This study shall be monitored according to a monitoring plan. The PI shall allocate adequate time for such monitoring activities. The PI shall also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit. The address is listed below. The monitoring procedures are a part of the sponsor's or its representative SOPs.

The monitoring shall be provided by a Canadian and Danish Clinical Research Organizations. Clinical Research Associates (CRA) will travel regularly to each site to perform the quality control of the data reported in the CRF.

6.2 Auditing and Inspecting

The trial may be subject to review by the EC/CA and/or to quality assurance audits performed by the sponsor or its representative and/or to inspection by appropriate regulatory authorities.

It is important that the PI(s) and their medical staff are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

7. DEVICE LABELING

See Appendix 10.

The Neuro Zti system is CE marked, Health Canada registered and distributed/sold into the market of participating countries.

The device shall be ordered by the hospital and billed to the social security organization and/or insurance company and/or relevant purchasing authority.

8. CONSENT MATERIALS

See Appendix 2.

All parties shall ensure protection of all subjects' personal data and shall not include subject names on any sponsors forms, reports, publications or any other disclosures. In case of data transfer, Oticon Medical shall maintain a high standard of confidentiality and personal data protection.

The informed consent form must be agreed to by Oticon Medical and the EC and must be in compliance with ICH-GCP, ISO 14155 standard, local regulatory requirements and legal requirements.

The investigator must ensure that each subject is fully informed about the nature and objectives of the trial and possible risks associated with participation. The investigator shall obtain written informed consent from each subject before any trial specific activity is performed. The informed consent form used in this trial, and any change made during the course of the trial, must be prospectively approved by both EC and Oticon Medical before use. The investigator shall retain the original of each subject's signed consent form.

9. Ethical Committee (EC)/Competent Authority (CA)

It is the responsibility of the investigator to have prospective approval of the trial protocol, protocol amendments, informed consent forms and other relevant documents from the EC/CA. All correspondence with the EC/CA shall be retained in the investigator file. Copies of the EC/CA approvals shall be forwarded by Oticon Medical or its representative.

The only circumstance in which an amendment may be initiated prior to EC/CA approval is where the change is necessary to eliminate an apparent immediate hazard(s) to the subjects. In such cases, the investigator shall notify the EC/CA and Oticon Medical or its representative within 5 working days after the implementation.

The trial shall be performed in accordance with the protocol, International Conference on Harmonization of Good Clinical Practice guidelines, the declaration of Helsinki (Appendix 11), ISO 14155:2011 standard and all applicable local regulatory requirements and laws.

10.ADDITIONAL RECORDS AND REPORTS

10.1 Data Handling and Record-Keeping

10.1.1 Case Report Form

As used in this protocol, the electronic Case Report Form (eCRF) should be understood to refer to an electronic data record depending on the data collection method used in this trial.

A CRF is required and should be completed for each subject. The completed original CRFs are the sole property of the sponsor. The CRFs shall not be made available in any form to third parties without written permission from the sponsor. Written permission is not required if the data is requested by the authorized representative(s) of the sponsor or an appropriate regulatory/legal authority.

It is the investigator's responsibility to ensure completion and to review and approve all CRFs. CRFs must be signed by the investigator or by an authorized staff member. These signatures serve to attest that information contained on the CRFs is true and correct. At all times, the investigator has final personal responsibility for the accuracy and authenticity of all clinical and test/exams data entered on the CRFs. Subject source documents are the physician's subject records maintained at the trial site. In most cases, the source documents are the hospital or the physician's chart. Where the source documents are the hospital or the physician's chart, the information collected on the CRFs must match those charts.

The eCRF cannot be considered as source document for this trial. Accurate and reliable data collection is ensured by the study monitor (source document verification).

The Electronic Data Capture system is compliant with the 21CFR part 11 FDA.

10.1.2 Subject Confidentiality

Information about the patients shall be kept confidential and managed according to the requirements of the Personal Data Protection law. Those regulations require a signed subject's authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to the information and why
- Who will use or disclosure that information
- The rights of the subject to revoke their authorization for use of their personal health information

Note: This information and the subject's authorization shall be provided to the subject in the informed consent form.

In the event that the subject revokes authorization to collect or use their information/data, the PI, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least safety status at the end of their scheduled study period.

To maintain subject confidentiality, the site number, the subject inclusion number and subject initials (SSID) will identify all study subjects on CRFs and all other documentation submitted to the Sponsor.

10.1.3 Source Documents

Source Data are the clinical findings and observations, laboratory and test data, and other information contained in the Source Documents.

Source Documents are the original records (and certified copies of original records); including, but not limited to, hospital medical records, physician or office charts, physician or nursing notes, subject diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, x-rays, CT Scans, MRI, etc. When applicable, information recorded on the CRF shall match the *Source Data* recorded in the *Source Documents*.

Study data shall be recorded directly on the CRF, whereupon the CRF data is to be considered the *Source Data*. Descriptions of these specific data shall be attributable, legible, original and accurate and must meet the regulatory requirements for recordkeeping. Source documents include all documents, images, files, and folders containing subject's medical data.

10.2 Record Maintenance and Retention

To enable evaluations/audits from regulatory authorities or Oticon Medical, the PI agrees to keep records, including the identity of all participants (e.g. Hospital records, CRFs, sufficient information to link records), all original signed informed consent forms, copies of all CRFs, serious adverse event forms, source documents and detailed records of device fitting/disposition. The records shall be retained by the PI according to ICH, local regulation, or as specified in the Clinical Study Agreement, whichever is longer.

If the investigator relocates, retires or for any reason withdraws from the study, the sponsor shall be prospectively notified. The study records must be transferred to an acceptable designee such as another investigator, another institution, or to the sponsor. The investigator must obtain the sponsor's written permission before disposing of any records, even if retention requirements have been met.

A unique subject identification code is assigned to each subject to protect subject identity. This unique code is used to identify the CRF, adverse events reports or other study-related data. These unique subject identification codes shall be recorded on the subject identification code list and kept in a confidential manner in the investigator site file. To protect subject identity, the subject names or other directly identifiable information shall not appear on any reports, publications, or other disclosures of clinical study outcomes.

10.3 Data Management Procedures

The data will be entered into a validated database. The sponsor or its representative shall be responsible for data processing, in accordance with procedural documentation. Database lock shall occur once quality assurance procedures have been completed.
All procedures for the handling and analysis of data shall be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

10.4 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks shall be implemented and applied to the database on a regular basis. Query reports (Data Clarification Requests) pertaining to data omissions and discrepancies shall be forwarded to the PIs and study monitors for resolution. The study database shall be updated in accordance with the resolved queries. All changes to the study database shall be documented.

10.5 Archival of Data

Appropriate backup copies of the database and related software files shall be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database. At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

10.6 Clinical Trial Registration

This trial shall be registered in www.clinicaltrials.gov, and results reported as required.

10.7 Publication

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, shall be published or passed on to any third party without the written consent of the study sponsor. Any PI involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

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12.APPENDIX

Appendix 1: Neuro Cochlear Implant System description
Appendix 2: PATIENT INFORMED CONSENT FORM
Appendix 3: ADVERSE EVENT REPORT FORM
Appendix 4: SERIOUS ADVERSE EVENT REPORT FORM
Appendix 5: EXPLANTATION REPORT FORM
Appendix 6: CLINICAL SUPPORT ROLE
Appendix 7: PATIENT HINT PERFORMANCE
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Appendix 10: DEVICE LABELING
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Appendix 1: Neuro Cochlear Implant System description

1.1 General description of device, intended uses, and model designations

The Neuro Zti cochlear implant system is a cochlear implant system consisting of the Neuro Zti implant, Neuro One sound processor and all components and accessories for the final user, and DigiMap software interface, and surgical tools for clinic.

The present technical file describes the “Neuro Cochlear Implant System”. The Neuro Cochlear Implant System is the fourth generation developed by Neurelec and the first cochlear implant to be developed and marketed by Oticon Medical. The intended use of the investigational device is to provide access to sound via direct electrical stimulation of the auditory nerve for adults and children suffering from severe to profound hearing loss. The Neuro Cochlear Implant system’s components (external and surgically implantable), electrical stimulation parameters and mechanism of action are essentially the same as approved predicate cochlear implant devices. The implanted component is the Neuro Zti receiver/stimulator with associated electrode arrays and the external component is the Neuro One sound processor. The implantable receiver/stimulator (Neuro Zti) may be configured with one of two different electrode arrays. The array model designations are the “Classic” array and the “EVO” array; the product configurations are labeled as Neuro Zti^{CLA} and Neuro Zti^{EVO}, respectively.

The device description herein has been modeled after guidance provided in the AAMI-CDV-4 CI86 guideline

The system including fitting interface, processor and implantable component are shown in figure 1 below:

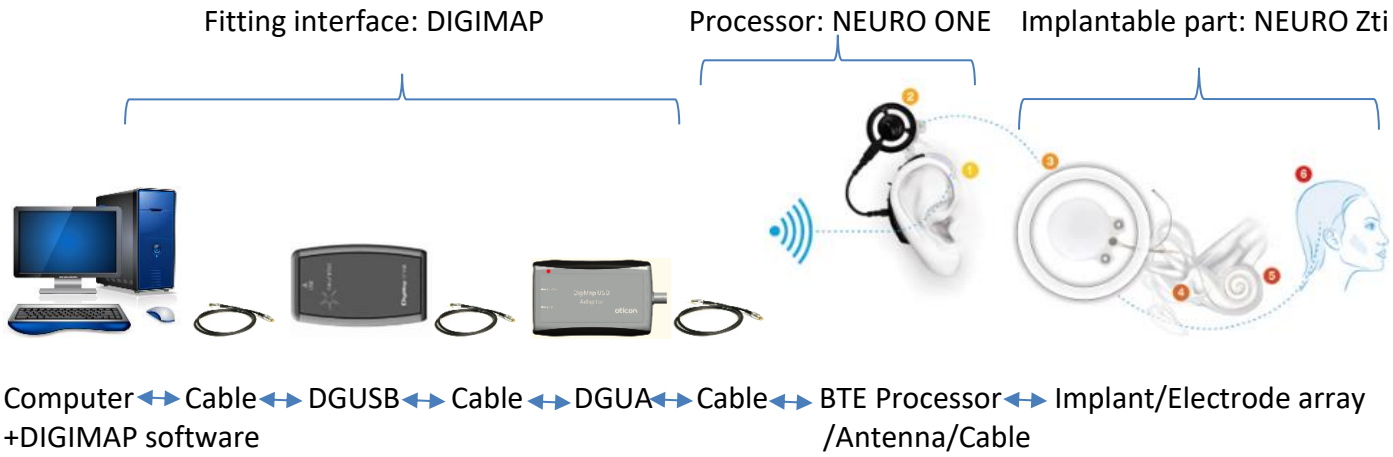


Figure 1: Schematic of the Neuro cochlear implant system including fitting components.

1.2 Specific inventory of system components and their essential functions

1.2.1 Implantable components

1.2.1.1 Receiver–stimulators

The system has a single receiver/stimulator model, The Neuro Zti. The Neuro Zti is designed to be surgically placed under the periosteum on the temporal aspect of the skull. Unlike predicate cochlear implant receiver/stimulators approved by the FDA, the Neuro Zti features an integrated fixation system which allows fixation to the skull using two self-tapping titanium screws. A schematic of the dimensions of the Neuro Zti can be seen in Figure 2. The Neuro Zti Cochlear Implant consists of electrical components hermetically encased within a mechanical housing made from zirconia and titanium. This housing is connected to a 20 contact multi-channel electrode-array with an integrated reference electrode located on the lead close to the receiver/stimulator. The feedthroughs in the housing enable the connection between the internal electronics and the electrode array. A unique design feature of the receiver/stimulator is that it has an opening in the center designed to securely hold a removable/replaceable magnet. The purpose of this feature is to allow magnet removal for increased MRI compatibility. In addition to being able to provide electrical stimulation to the cochlea, the Neuro Zti is equipped with circuitry to enable use of the electrode contacts for the recording of electrically evoked compound action potentials (eCAPs).

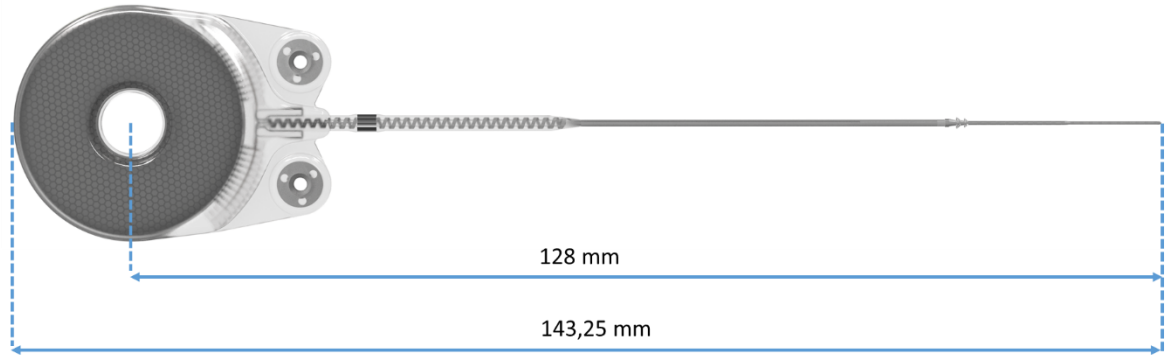


Figure 2: Schematic of the Neuro Zti configured with the "Classic" array (Neuro Zti^{CLA}). Dimensions are in millimeters unless otherwise noted.

1.2.1.2 Electrodes

The Neuro Zti may be configured with either the "Classic" or "EVO" array; these two product configurations are designated as Neuro Zti^{CLA} and Neuro Zti^{EVO}, respectively. A schematic of the two electrode options can be seen in Figure 3, while detailed information regarding the arrays is further outlined in Section 1.5. The arrays are both constructed from the same raw materials with the contacts being machined from platinum/Iridium (10%). The wires between contacts and the receiver/stimulator are coated with PTFE for electrical isolation. The PTFE coated wires are completely embedded inside an over-molding comprised of medical grade silicone; therefore, the wires are not in contact with the tissues.
The principal differences between the two electrode array options are that the Neuro Zti^{EVO} has a slightly smaller form factor allowing for reduced stiffness and may be more suitable for "softer" surgery. Both arrays are currently approved for use in Canada and the European Union and have been used with the prior generation device, Digisonic SP. The company makes no specific warrantee or prescription as to which array is most appropriate for a given patient; thus leaving the array choice to the preference of the surgeon. Furthermore, there are no specific restrictions as to the surgical approach to the cochlea (ie. traditional mastoidectomy vs transtympanic approach) or to the introduction of the array into the cochlea (round window vs cochleostomy approach). Both arrays may be inserted (and re-inserted if necessary) into the scala-tympani using the same techniques.

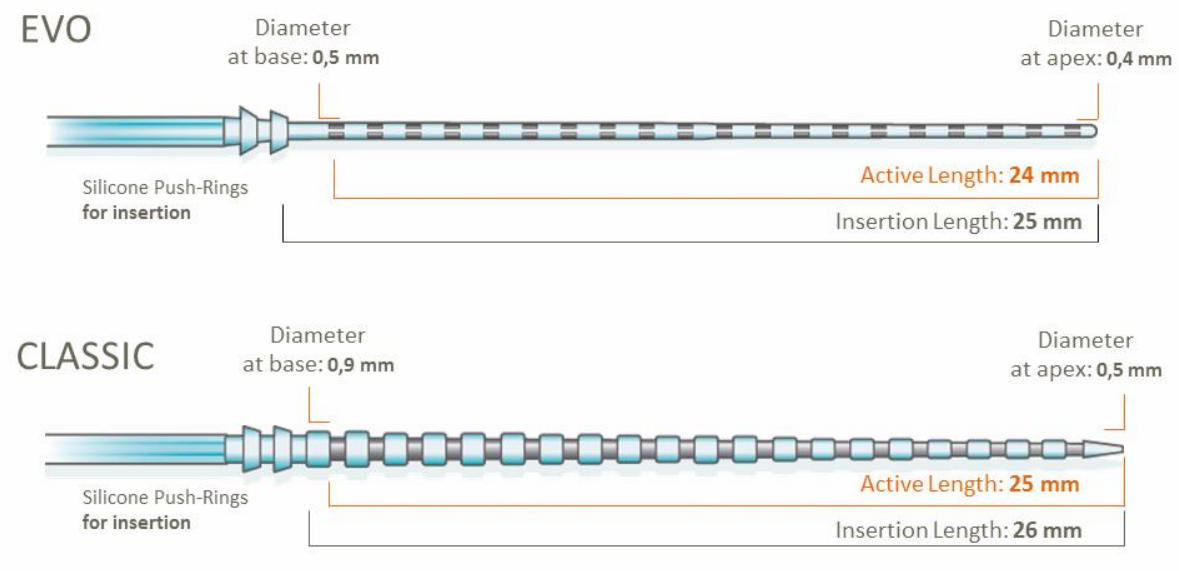


Figure 3: Schematic showing the EVO and CLASSIC electrode array options for the Neuro Zti

1.2.1.3 Connector systems

The system does not include a percutaneous connector. Communication between the external and implanted components is accomplished via an inductive link. The mechanical stability of the connection is made possible by magnetic coupling between the implanted magnet and the magnet inside the external coil.

1.2.2 Non-implantable components

1.2.2.1 Sound processors and body-worn accessories

The sound processor for the investigational device is called the Neuro One (see Figure 4). The Neuro One enables the functionality of the Neuro Zti by delivering the power and data required for electrical stimulation of the cochlea. Without the external processor, the implanted components will not function. The Neuro One is powered by two Zinc-air batteries with electrical components housed within a mechanical design to enable the patient to wear the processor behind the ear (BTE). The inductive link to the implanted Neuro Zti is established using an external coil connected to the Neuro One via a replaceable cable. The external coil also contains a magnet, which couples with the magnet of the implanted Neuro Zti to keep the external coil in place. Magnet strength may be adjusted to improve retention and/or reduce the risk of skin-flap complications.

FIGURE 4

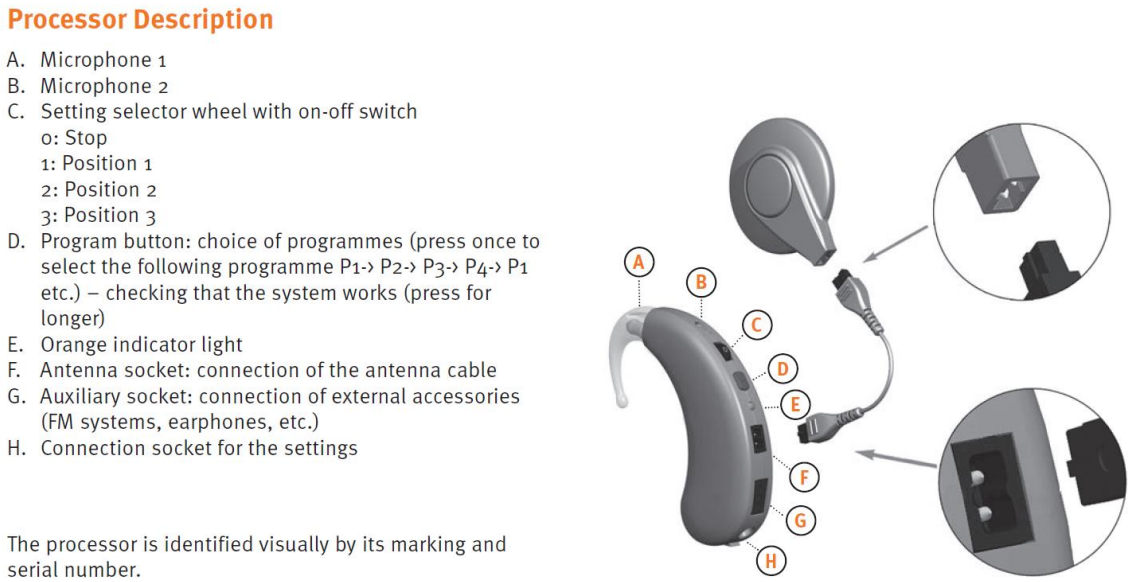


Figure 4 shows a schematic illustrating the mechanical design of the Neuro One sound processor. The principal components and their associated functions are labeled and indicated in the processor description on the left.

1.2.2.2 Non-body-worn accessories and replaceable body-worn components

It is planned that the commercial version of the Neuro One processor will be packaged with essential accessories, components and associated documentation. Figure 5 shows and describes the non-body-worn accessories and replaceable body-worn components included with the Neuro system.

Packaging contents

1. Neuro One Processor x 1
2. Antenna with magnet x 1
3. Antenna Cable x 1
4. Case x 1
5. "Perfect Dry" heating desiccation drying box x 1
6. Zinc-Air battery boxes x 3
7. **Accessories box x 1 containing:**
   - 7.a Additional antenna cable x 1
   - 7.b Additional antenna x 1
   - 7.c Additional magnet x 1
   - 7.d Additional earhook x 4
   - 7.e Holding buckle x 1
   - 7.f Set of earphones x 1
   - 7.g Screwdriver x 1
8. **Carry case x 1 containing:**
   - 8.a Cleaning wipes x 2
   - 8.b Cover Clip x 1
   - N-A 6 Battery blister pack x 1
9. USB memory stick for backing up the settings that also contains the Accessories user manual (9.a) x 1
10. Processor User Manual x 1
11. Processor registration form (activation of the warranty) x 1
12. Silhouette x1
13. Stickers for identification Right/Left

N-A Other documents N-A

Pictures are not contractually binding

Figure 5 shows and describes the components and accessories included in the Neuro One patient kit.

1.2.2.3 *Body-worn and non-body-worn cables*

The Neuro One sound processor requires a cable between the processor and the external coil. The cable is replaceable, comes in a single length and is illustrated in Figure 5 #3. In addition to the antenna/coil cable, the Silouette (Figure 5 #12) includes an integrated cable used to communicate to the Neuro One via telecoil input.

1.2.2.4 *Components for system clinical support (e.g., clinical programming pods, clinical mapping software, test materials)*

External communication with the Neuro One is necessary for programming the processor and performing certain diagnostic testing (Impedance measures, ECAP measures, EABR and ESRT trigger outputs). This communication requires a Windows PC with a USB port, USB cable, a programming interface box with electrical isolation and a mini-din 6-pin cable to complete the connection from the interface box to the Neuro One. The general specifications of the Programming interface box are outlined in Table 1. In addition to the aforementioned hardware, PC compatible software, called DigiMap, is necessary to program and configure the Neuro One processor.

TABLE 1: Specification of the Programming Interface Hardware

Power	5 Volts/300 mA (via USB)
Protective Fuse	500 mA
PC Interface	USB (compatible with USB 1.1, 2.0 and 3.0)
External Trigger	Connector : BNC Output Range : 0V to 5V Pulse Duration: 50 µs Safety : Electrical Isolation via Capacitive coupling Control: Via DigiStim PC Software
Weight	208 g
Dimensions	10.2 cm X 18.8 cm
Temperature	Functioning: 0-40C Stock/Storage: -10-55C

1.2.2.5 Components for surgical support (e.g., insertion tools, templates)

The components of the system intended to support surgical placement and fixation of the implantable components are shown in figures 6-8 below.

FIGURE 6

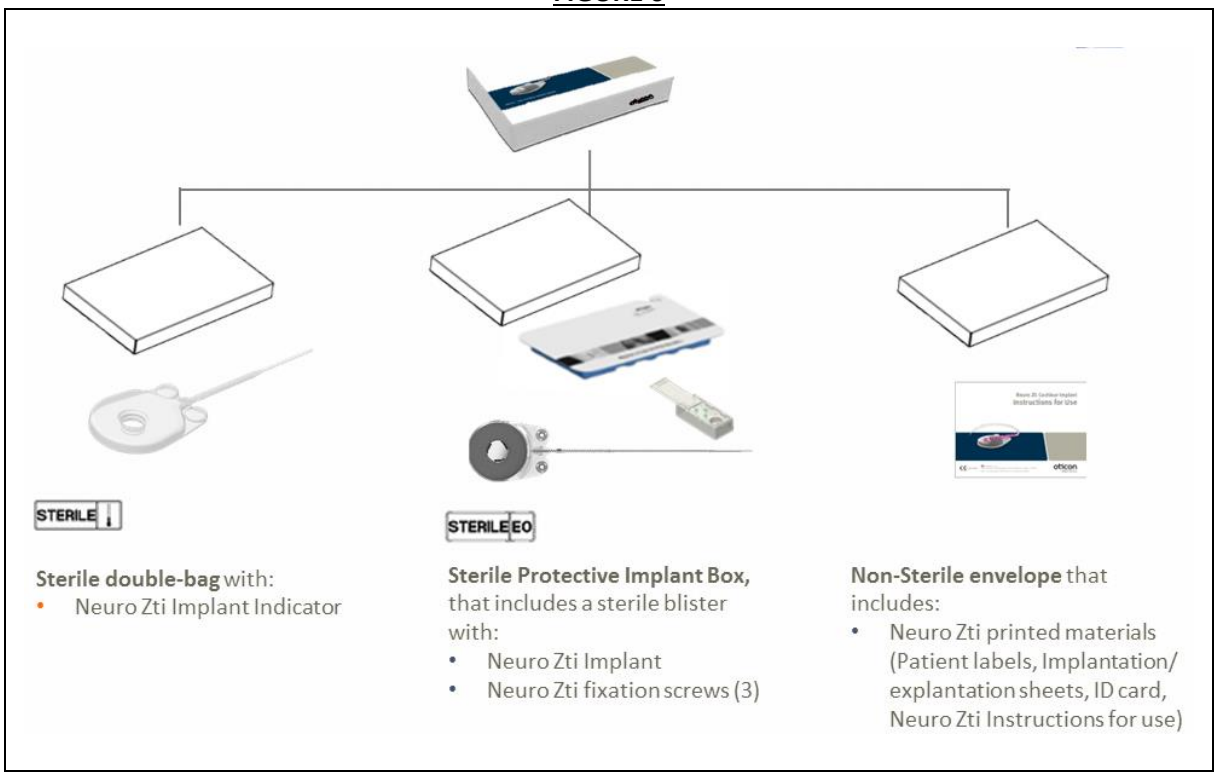


FIGURE 7

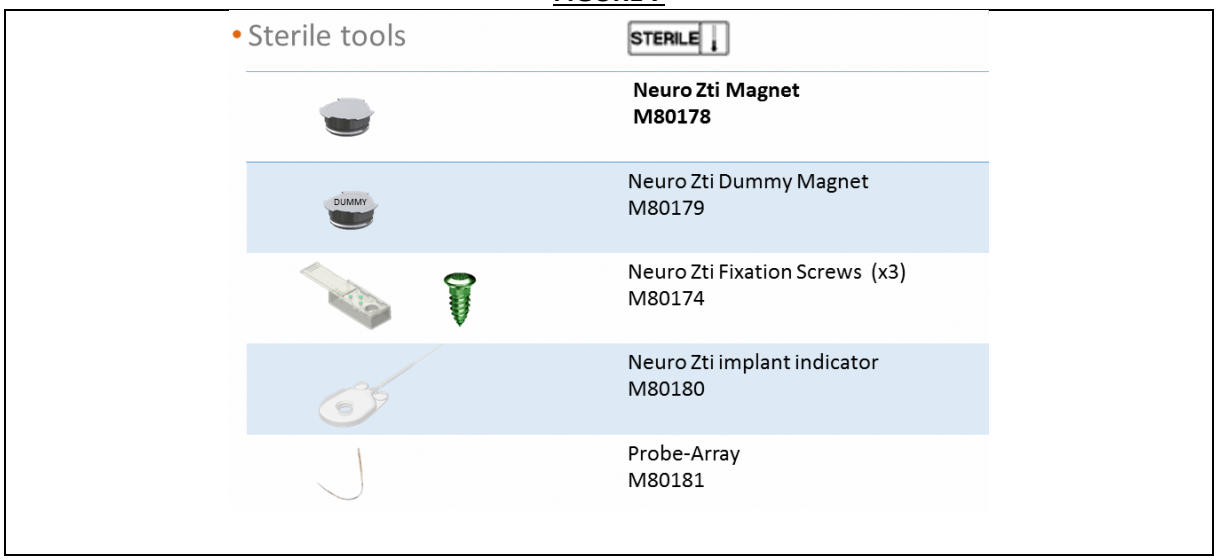
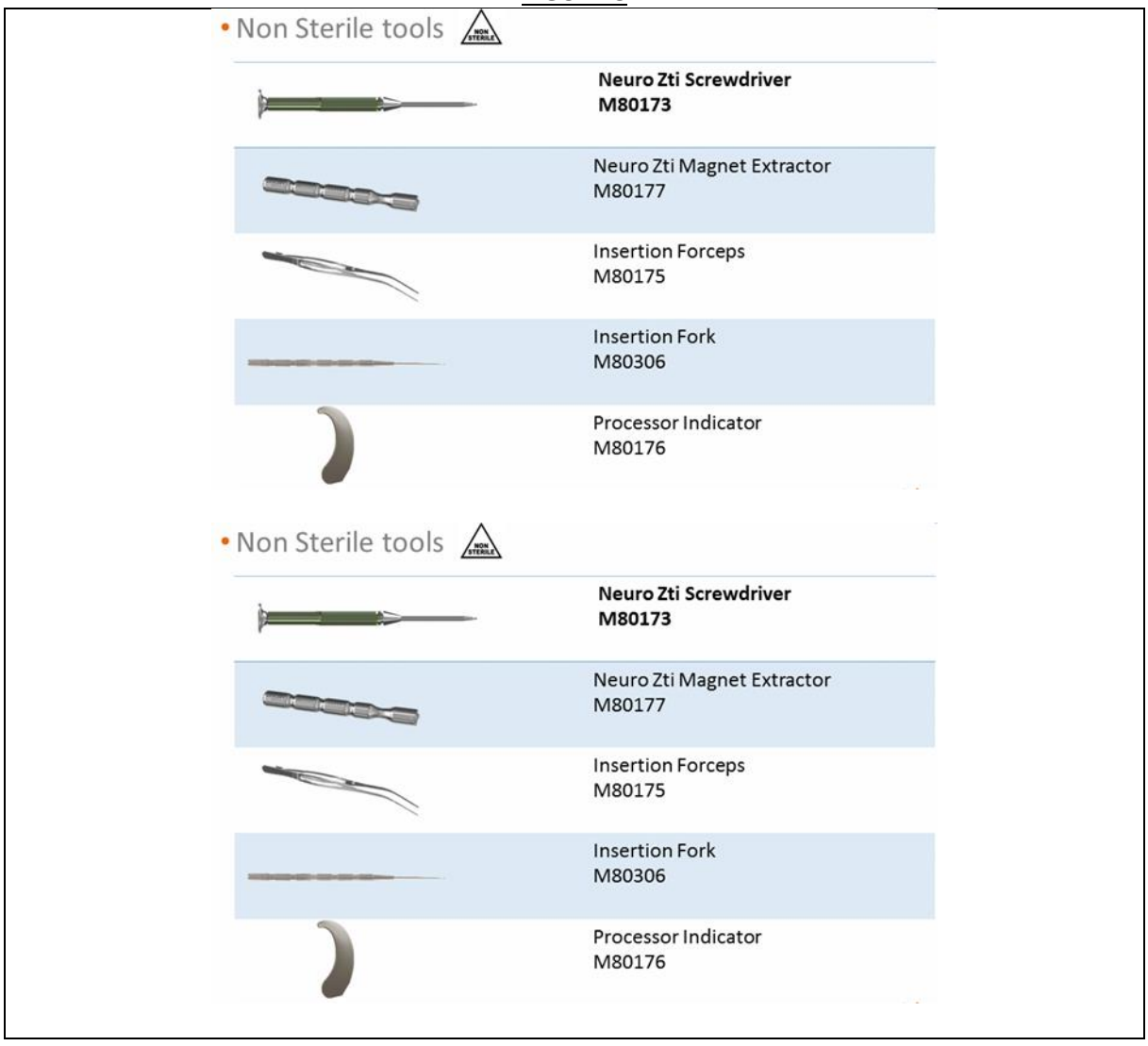


FIGURE 8



1.3 System software and processing strategies

The processing strategies of the Neuro Cochlear Implant system utilize square-wave charge-balanced pulsatile non-simultaneous stimulation protocols. For the sound coding strategy, the incoming sound is converted into the spectral domain using an FTT. Essentially, the stimulation strategy is what is known in the field as an "N of M" strategy, meaning N electrodes are activated from M electrodes per frame. Unique to the Neuro system, the wide input dynamic range per sample is not compressed until the final stage of processing. Furthermore, the compression mapping is divided into four frequency (electrode) groups. This final stage multi-band compression is designed to avoid transient artifacts and cross-modulation frequency distortion inherent in broad-band automatic gain control strategies that operate in the time domain.

1.4 Essential features of sound processing hardware

TABLE 2: Technical Specifications of the Neuro One Processor

Mechanical Properties	
Dimensions	50.5 x 50 x 10.6 mm
Weight	11.4 g (with batteries)
Characteristics	
Colors	7
Number of Magnet Strength Options	8
Cable Lengths	2
Condition Of Use	
Operating Temperature Range	5° C to 40° C
Moisture Resistance	0 to 90 %
Atmospheric pressure	700 hPa to 1060 hPa
Packaging And Storage	
Storage Temperature Range	-20° C to 50° C
Moisture Resistance	0 to 90 %
Atmospheric pressure	700 hPa to 1060 hPa
Microphones	
Number	2
Automatic Adaptive Directionality	Yes - Free Focus offers : • 3 directionality modes (Full, Split, Omni) • 2 adaptive modes (Auto-Tri, Auto-Dual)
Input Dynamic Range (IDR)	25 dB SPL – 115 dB SPL (programmable range: 23 dB SPL to 95 dB SPL)
Sound Processing	
Automatic Environment Detection	Yes
Audio Sound Capture	18 bits resolution
Sound Input Frequency Range	Up to 8333Hz
Effective Audio Sampling Rate	16667 Hz – 3 input sources with up to 2 parallel input sources
Gain Management	Yes - Voice Guard back-end multiband compression
Maximum Stimulation Rate	47500 pps, Software limited to 37500 pps
Supported Strategies	"NEW STRATEGY NAME"/CRYSTALIS^{XDP} / MPIS^{XDP}
Noise Reduction Features	Voice Track, Wind Noise Reduction
Speech Enhancement Features	Voice Guard, Free Focus

Audio Inputs	
Telecoil	Yes – In built
Direct Connection	Yes – Universal (FM, auxiliary inputs)
Bluetooth	Yes – Using Telecoil with 3rd party system
User Interfaces	
Program push button	Up to 4 programs
Wheel Selector	On/Off – Sensitivity control ± 6 dB
Diagnostic Tools	
Indicator Light	Orange indicator for program selection, start-up test, stimulation status, battery status, and error conditions – Can be disabled by audiologist.
Private Beeps	Sound indicator for self-check test, program selection, battery status, and error conditions - Can be disabled by audiologist
Self-Check Diagnostics	Integrated full system diagnostics (processor, cable, antenna) – Easy operating using push button
Neuro ECAP 1.0 Telemetry	Patented Masker Probe ECAP detection with efficient artefact cancellation Integrated DSP high sampling rate system up to 200 samples Programmable stimulation rate 21Hz to 83Hz Programmable number of recording electrodes
Other implant measurements	EABR, ESRT, impedances

1.5 Electrode specification and characteristics

As previously mentioned, the Neuro Zti may be configured with one of two different electrodes. Tables 3-4 describe the details for the Classic and EVO arrays, respectively.

TABLE 3: Specifications and characteristics of the Neuro Zti^{CLA}

Identification number	M80184
Material components	Connecting wire: Platinum iridium 10% Stimulation electrode: Platinum iridium 10%
Number of independent active electrodes	20
Insertion length	26 mm
Active length	25 mm
Dimensions	Active area: 0.39 mm² to 0.77 mm² Diameter at apex: 0.5 mm Diameter at base: 1.07 mm
Reduced cochleostomy size	Diameter of 1 mm (may be inserted via round window)
General shape	Straight Straight: distance between electrodes and silicone, inferior to 0.1 mm
Shape at apex	Rounded shape
Shape at the base	Diameter push rings: 2x1.5 mm
Insulation	PE (polyester): wire Si (silicone): external tubing

TABLE 4: Specifications and characteristics of the Neuro Zti^{EVO}

Identification number	M80185
Material components	Connecting wire: Platinum iridium 10% Stimulation electrode: Platinum iridium 10%

Number of independent active electrodes	20
Insertion length	25 mm
Active length	24 mm
Dimensions	Active area: 0.46 mm² to 0.60 mm² Diameter at apex: 0.4 mm Diameter at base: 0.5 mm
Reduced cochleostomy size	Diameter of 0.8 mm (may be inserted via the round window
General shape	Straight Straight: distance between electrodes and silicone, inferior to 0.1 mm
Shape at apex	Rounded shape
Shape at the base	Diameter push rings: 1x1.5 mm & 1x1.2 mm
Insulation	PE (polyester): wire Si (silicone): external tubing

1.6 Stimulation methodology and provisions for safe stimulation

1.6.1 Stimulation Circuitry

A general description of the specifications of the internal components can be found in table 5.

TABLE 5: Technical Specification of the Neuro Zti Cochlear Implant

Stimulation capacity	
Primary function	Cochlear implant
Stimulation mode (depending on configuration)	Anodic with Common Cathodic Ground, biphasic monopolar, biphasic multipolar in sequential or simultaneous modes
Maximum stimulation rate	47500 pps, Software limited to 37500 pps, default 20800 pps
Objective measurements	Impedance measurement Measurement of the implant's power Electrically evoked compound action potential (eCAP) Psychoacoustic tests (gap, test, etc.) Identification
Electrode Array options	Classic or Evo (see Tables 3-4 for array specifications)
Independent output circuits	24 (20 used in current configuration)
Radio Frequency Telemetry	6.78 MHz (bi-directional)
Surgical approach	In accordance with standard/routine clinical practice with no specific restriction
Mechanical properties	
Weight	10.5 g
Dimensions	Diameter: 30.5 mm. Thickness: ranging from 4.0 mm (center) to 4.5 mm (edge)
Volume	4.15 cm^3
Integrated Fixation System	2 self-tapping titanium screws with typical penetration depth of 1.73 mm below the surface of the implant
Material in direct contact with human tissue	LSR 40 shore A silicone HCR 35 shore A & HCR 50 shore A silicone Adhesive silicone Platinum iridium 10% Titanium grade 2 Titanium grade 5
Receiver	Titanium base – encapsulation in Zirconia

Insulation	PE (polyester): wire Si (Silicone) : external tubing	
Implanted Components	Hermetically sealed receiver/stimulator connected to an electrode array	
Performance characteristics		
Characteristics of the output signal (on resistance of 1 kΩ)	Max 2V – 255 µs	Charge: 5nC – 200nC
Independence measurement	Normal values: 500 Ω – 7 kΩ	
Safety		
Communication security	Unique implant identification (ID) is paired to a specific external processor	
Maximum Charge Density	<50µC/cm² (Neuro ZTI^{EVO}) <59µC/cm² (Neuro ZTI^{CLA})	
DC Current Prevention	Blocking Capacitors for each output circuit, software programmable shorting between stimulation frames and/or between individual pulses	
MRI safety level	Compatible 1,5 Tesla with the magnet in place. Compatible with 3 Tesla (after removing the magnet).	
Ionizing Radiation	Dose max 112 Grays	
Methods recommended for determining the proper functioning of the system	Impedance measurement and integrity test (with collection equipment)	
Operating pressure	Absolute pressure of 3 bars (corresponding to a diving depth of 20 meters)	
Reference electrode	1 cylindrical ground electrode – 17 mm². Diameter: 2.1 mm. Length: 2.5 mm	
Impact Resistance	≥ 2.5 Joules	
Packaging And Storage		
Storage Temperature Range	-30°C to +60°C	
Moisture resistance	0% to 90%	

Appendix 2: PATIENT INFORMED CONSENT FORM

SUBJECT INFORMATION AND CONSENT FORM

Title of research: « The Neuro Zti Cochlear Implant System Efficacy and Safety in Adults »

Protocol n°: PIC_07

Sponsor: Oticon Medical, 2720 Chemin Saint Bernard 06224 Vallauris, France.

Investigator: [*name and contact information]*

1. SUMMARY

You are being asked to participate in research study. The purpose of this consent form is to help you decide if you want to participate in the research study.

You should not join this research study until all of your questions are answered.

Things to know before deciding to take part in this research study:

- The main goal of a research study is to confirm/endorse efficacy and safety of the Neuro Zti cochlear implant system to help patients in the future.
- The decision to join or not join the research study will not cause you to lose any medical benefits. If you decide not to take part in this study, your doctor will continue to treat you.
- Parts of this study involve standard medical care. Standard care is the treatment normally given for a certain condition or illness.
- Other parts of this study involve an investigational device that is being tested according its intended use. In this study, the investigational device is a cochlear implant CE marked and approved in the different participant's countries. CE marking means that the product conforms to all EU directives and EU regulations that apply, it is also Health Canada approved.
- After reading the consent form and having a discussion with the research staff, you should know which parts of the study are experimental and which are standard medical care.
- Your medical records may become a part of the research record. If that happens, your medical records may be looked at and/or copied by the sponsor of this study and/or health agencies associated with the study.
- Your usual care cost such as cochlear implant device, surgery, hospital stays, audiometric tests, imaging exam(s) that you receive whether or not you were participating in this study will be covered by your health care system and/or medical insurance The sponsor will pay extra care costs or a lump sum, associated with this study, directly your hospital. Taking part in a research study would not affect your current or future health care and/or medical insurance coverage.
- If you take part in this research study, you will be given a copy of this signed and dated consent form.

2. PURPOSE OF THE STUDY

The Neuro Zti Cochlear implant System is indicated for severe to profound deafened individuals. It includes both external and implantable components. Surgery is required to place the implanted part (the Neuro Zti Implant) while the external components (Neuro One sound Processor) are worn behind the ear. A small antenna coil connected to the Neuro One Sound Processor is used to deliver both power and information to the implanted Neuro Zti. Using an electrode array, the Neuro Zti provides direct electrical stimulation to the hearing nerve to restore the perception of sound.

This cochlear implant is already approved in the different countries and placed on the market in Europe and Canada. The system is CE marked and Health Canada approved, and has been sold in Europe and in major parts of world since September 2015. This cochlear implant meets the essentials requirements of medical device regulation focus on its safety and its efficacy.

The purpose of this study is to systematically collect efficacy and safety data that can be leveraged to expand access of Neuro CI Technologies to other countries under different regulatory jurisdictions.

To test the efficacy of the device several audiometric exams will be done to assess your auditory performance over time. In addition, the safety of the device will be monitored throughout the study and thereafter within the required manufacturer vigilance framework.

3. WHO CAN TAKE PART IN THIS STUDY?

To take place in this study you must:

- be determined to be a candidate for cochlear implantation
- choose to be implanted with the Neuro Zti
- understand the study requirements and associated constraints and
- provide informed consent

You should not take part in this study if you do not meet all requirements.

You cannot participate if

- You have an inflammatory disease of the middle ear disease or other medical conditions such as auditory nerve lesions, pathologies of central auditory pathway, cochlea malformation or ossification.
- You are unable or unwilling to use the cochlear implant system appropriately or to comply with all study requirements.
- You have unrealistic expectations regarding the possible benefits, risks and limitations inherent to the surgical procedure.
- You have not had an appropriate meningococcal meningitis vaccination or not updated.

4. WHAT DOES THE STUDY INVOLVE?

4.1. Study plan

The study plan seeks to enroll a total of 55 subjects.

Your participation in this study is expected to last until the completion of the study or until you and/or your doctor decides that there is no clear benefit for you to continue the study. However, your doctor will request regular follow-up visits and will also monitor to your health status. The expected minimal trial duration is approximatively 14 months.

If you decide to take part of this study, the procedures and visits you can expect are described in section 5.3. This will give you information about what taking part in the study will require from you, for example how often you have to come to see the doctor as well as what tests and procedures will be performed.

4.2. Treatment assignment

All participants will be implanted with the Neuro Zti implant and use the Neuro One sound Processor.

After the study ends, you will be followed as a standard cochlear implant patient in a routine care framework.

5. PROCEDURES OF THE STUDY

All subjects consenting to participate in this study are to be implanted with the Neuro Zti cochlear implant.

5.1. Standard care procedures

- Surgery methodology and anesthetic care
- Postoperative care
- Visit appointments are set on the standard care visits
- Postoperative programming and auditory rehabilitation.
- Objectives measurements such as electrode impedance measures are routinely performed during cochlear implantations and thereafter during fitting sessions. These measurements are used to check electrode-array integrity and are useful in the monitoring of implant functioning.

5.2. Exploratory procedures

The assessments used are those commonly used in standard practice of cochlear implant rehabilitation program.

- *Audiometry assessment with HINT (Hearing In Noise Test) sentences.* The HINT measures the person's ability to hear speech in quiet and in noise, it is used in routine audiological practice. Even though the assessment of your hearing can be done with different test, the HINT provides an efficient and reliable method for assessing person hearing across different languages.
  Pre-operatively, the HINT test will be performed with your hearing aid(s) in the best fitted conditions, and post-operatively, only your implanted ear will be tested.

- *Objectives measurements eCAP (electrically evoked Compound Action Potential).* The eCAP measures are readily available in the clinical software of all cochlear implants on the market

for measuring auditory nerve responses to electrical stimulation. The Neuro Zti ECAP features and functionality may be evaluated at the end of your surgery and at follow-up visits.

You will be asked at each visit about your health status and if any adverse events occurred since your last visit.

You will be asked to complete a patient diary to collect information on the period of device use, any issues related to non-device use and miscellaneous comments.

5.3. Schedule visit procedures

Visit 1 (screening visit, 8 weeks before surgery)

- Candidates for cochlear implantation may be candidates to participate in this research study.
- Screening may be done during a medical visit, by telephone, by mail or through medical records.
- This screening process may determine if you are an appropriate candidate for this study (e.g. motivation, geographical remoteness, willing to commit protocol requirements).
- You should be informed with the inform consent form and you should be given sufficient time to consider your decision and to clarify any questions you may have.

Visit 2 (inclusion visit, 4 weeks before surgery)

No study procedure can be performed without your signed consent form.

- Your Informed consent is obtained
- You will be assigned a single subject identifier (SSID) by the sponsor
- Your physician will make sure that you have appropriate hearing aid settings to be in the best aided condition according to the clinical practice
- Inclusion/exclusion criteria will be reviewed
- Demography, medical history and concomitant medications will be reviewed
- Audiometric evaluations with HINT test in Quiet and in Noise will be performed
- Cochlear implantation scheduling will be confirmed

Visit 3 (cochlear implant surgery)

Surgery shall be performed according the conventional cochlear implantation procedures and standard surgical practice.

- Time of surgery will be recorded
- Objective measures: electrode impedances and ECAP
- Complications/adverse effects collected
- Concomitant medications collected

Visit 4 (follow-up visit, 2 weeks after surgery)

- Clinical examination (general state, scarring) performed
- Complications/adverse effects collected
- Concomitant medications collected

Visit 5 (cochlear implant activation, 1 month after surgery)
- Activation and fitting of your cochlear implant
- Objective measures: electrode impedance
- Complications/adverse effects collected
- Concomitant medications collected
- Patient diary issued

Visit 6 (follow-up visit, 3 months after implant activation)
- Audiometric evaluations with HINT test in Quiet and in Noise
- Objective measures: electrode impedance and ECAP
- Fitting of your cochlear implant
- Complications/adverse effects collected
- Concomitant medications collected
- Previous patient diary collected and new patient diary delivery

Visit 7 (follow-up visit, 6 months after implant activation)
- Audiometric evaluations with HINT test in Quiet and in Noise
- Objective measures: electrodes impedance and ECAP
- Complications/adverse effects collected
- Concomitant medications collected
- Previous patient diary collected and new patient diary delivery

Visit 8 (end of study, 12 months after implant activation)
- Audiometric evaluations with HINT test in Quiet and in Noise
- Objective measures: electrodes impedance and ECAP
- Complications/adverse effects collected
- Concomitant medications collected

  Previous patient diary collected

Unscheduled visit(s), may be done at any time during the study
- Complications/adverse effects collected
- Concomitant medications collected
- Objective measures: impedance and ECAP, where appropriate

6. POTENTIAL RISKS

Risks

Electrical stimulation of the hearing nerve with cochlear implants has been in use for over 30 years without any report of damage to tissue resulting from electrical stimulation. If problems should develop in the future, the implant can either be not used or surgically removed.

The rate of complications associated with cochlear implant surgery is small and post-complications are rare but it is critical that you review and understand the potential risks prior to singing the informed consent.

Potential risks include but are not limited to:

- Risks associated with general anesthesia: include but are not limited to lightheadedness, nausea, skin rash, constipation, death.
- Risks associated with surgery: include but are not limited to dizziness, vertigo, dryness of the mouth, ringing (tinnitus) in the ear, partial or complete facial nerve paralysis, pain near the implant, numbness near the implant, changes in taste perceptions, death.
- Meningitis is a rare but potentially serious complication. To minimize the increased lifetime risk with a cochlear implant you must be properly vaccinated and know the symptoms of meningitis to minimize the time between symptoms and treatment should they ever occur.
- There is a risk that you may have some bleeding after the operation. Complications associated with bleeding or healing may require local treatment and/or more invasive surgical intervention.
- You may experience numbness and/or stiffness occur around the ear. In most cases, such symptoms improve gradually over time but may not completely disappear.
- You may have some loss of taste on the side of the operation, which may be temporary or permanent
- Rarely, you may have some temporary weakness of your facial muscles that may result from swelling near the facial nerve. Such symptoms typically resolve within several weeks, but permanent paralysis may occur.
- Your wound may become infected and may require local and/or systemic antibiotic therapy. It is possible that the skin wound may fail to heal and the device may need to be removed.
- You may have some pain in the area of the coil, which generally improves over time.
- It is possible that your body may reject the implant, which may result in extrusion of the implant and/or necessitate surgical intervention to remove the device.
- The external equipment may be fail and/or require re-mapping
- The internal device may be fail requiring the need for a second surgery to replace the damaged device. You will need to avoid sports and activities where there is a potential to damage the device.
- Prior to undergoing any other medical or therapeutic intervention you must inform the medical staff that you have a cochlear implant, as some procedures or investigations may damage the device and/or expose you to serious risk of injury or death.
- There may be circumstances where it may not be possible to insert the implant electrodes completely and this may have a negative impact on potential outcome.
- There is a risk that modern imaging will be unable to determine the integrity of your auditory pathways and their ability to processes electric stimulation. The ability of the implant to

improve speech perception will depend on the existence and ability of auditory nerve to conduct impulses. The functional integrity of the pathways is known to impact outcome and is difficult to predict in advance.

- It is impossible to predict in advance how well you will perform with a cochlear implant. It is important for you to understand that a cochlear implant will not cure your deafness nor will it completely restore or provide normal hearing.
- You should take care to avoid static electricity. Static electricity may damage the electronic components of the device or the programs.

Even though the Neuro Zti has approval for certain MRI conditions, there are risks associated with an MRI exam, as for all other cochlear implants. Therefore, prior to undergoing any MRI exam for any part of your body, you must inform the physician that you have a cochlear implant and present your implant identification card. Even optimal conditions, during an MRI exam it is possible that you may experience discomfort and/or auditory sensations such as cracking, beeping and/or humming sounds. Should you experience discomfort during an MRI exam it is important to notify the clinician immediately.

Should other medical therapies be considered, please consult your identification card and/or a qualified clinician prior to therapy. In addition, please take notice of the Neuro One processor instructions for use.

7. NEW INFORMATION

You will be told about any important new information that is found during the study that might affect your health, well-being or willingness to stay in the study. You may be asked to sign a new consent form if this occurs.

8. BENEFITS

Your speech perception and hearing skills may be improve following cochlear implantation. The improvement depends upon many factors which have been explained to you by the investigator and your medical team.

The results of this study may be help people with severe-to-profound hearing loss in the future and may be used to improve the cochlear implant system.

You do not to have to take part of this study to be treated for your deafness. You may also benefit from the Neuro cochlear implant system in routine care without enrolling in the study.

9. COMPENSATION FOR INJURY

Health care is provided through a system of national or provincial insurance depending on your country.

This insurance may or may not provide coverage for certain types of injuries that might result from taking part in the study. To this extent:

Oticon Medical will provide the study over-costs free of charge during the study (experimental tests and procedures). Standard tests and procedures that are done for the study that would also be done

for a standard non-study patient will not be billed to you but billed to the health care system and/or your insurance company.

The health care system and/or your insurance company may be billed for:

- Any standard medical given during this research study
- Other specific local reasons.

You may want to talk with your insurance company about payment policy for standard medical care given during surgery. If your insurance company does not pay, you may be billed for those charges.

You might have unexpected expenses from being in this study. Ask your study investigator to discuss the costs that will or will not be covered by the sponsor. This discussion should include who will pay the costs of treating possible side effects.

Signing this form does not mean you that you have given up any of your legal rights. The investigator, sponsor or hospital would still have legal and professional responsibilities to you.

10. COSTS

Your cochlear implant will be provided by the hospital as any conventional cochlear implant and billed to health care system and/or your insurance company.

For unscheduled visits, you might have to pay for some expenses related to your taking part in this study, such as transportation, parking, others. You will be reimbursed of up to 100€/study visit for expenses related to your taking part in this study only if the unscheduled visit is related to side effects related to the cochlear implant. This does not include side effects related to surgery or medical reasons other than related to the device.

11. WHO DO I CONTACT IF I WANT TO REPORT HEALTH PROBLEM OR HAVE QUESTIONS?

If you have any injury, side effects or any unusual health experience during this study, make sure that you tell the investigator or study staff immediately. You may call at any time to report an adverse event.

If you have any questions or concerns about this study, your rights, please contact your investigator:

[Name+Contact phone investigator]: _____

Do not sign this informed consent document until all of your questions and concerns have been addressed.

12. VOLUNTARY PARTICIPATION AND WITHDRAWAL

Your taking part in this study is entirely voluntary. Whether or not you take part is completely up to you. You will continue to receive the best possible care no matter what you decide.

If you choose to take part and later change your mind, you may do so. You may stop participating at any time. A decision to stop being in the study will not affect how your health care is provided to you. If you decide to stop the study, please inform the investigator and/or one of the staff involved in the

study. Should you decide to withdraw, you can arrange follow-up care with your physician and/or clinic staff.

The investigator and the sponsor reserve the right to, at any time and for any reason, either withdraw you and/or stop the study independent of your desire to continue. This could happen if you experience serious side effects, have a serious adverse event and/or if there is new information about the safety and effectiveness of the Neuro Zti cochlear implant system. The investigator or its study staff will explain the reason(s) for any early termination and arrange for your continued healthcare.

13. ALTERNATIVE TREATMENT

The Cochlear implant is designed to treat severe-to-profound hearing loss. There are other cochlear implants commercially available. The investigator can discuss these possibilities with you.

14. AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

The investigator and study staff will handle your personal health information in a confidential manner and in compliance with applicable law. Your health information will be used and disclosed as defined in the following data privacy statements.

In this section “personal health information” means information about a person that relates to things like the person’s physical and/or family health history, health care, health care provider and information that directly identifies the person (name, date of birth, address etc.). The term “study data” means study-related health information that does not directly identify a person (that is, does not contain the person’s name, address, health number or other identifying information) but that does contain an assigned code number for the person and the person’s initials.

By signing the consent document for this study, you will be giving permission for the use and disclosure of your personal health information that are described in this data privacy statement. If you do not wish to allow the disclosure and use of your personal information as described herein, you should not participate in this study.

If you agree to participate in this study, your personal health information and study data will be maintained, used and shared in the following way:

- The study monitor, study auditor, the sponsor’s clinical research staff and regulatory authorities might have access to your personal health information. This may include information from your health records such as medical history, auditory test results, special reports and medications that you have had in the past and/or are currently undergoing. Your records will be kept and disposed of in accordance with applicable laws and regulation.
- The investigator and their study staff will send your study data to the sponsor, and/or its associated representatives. Because the sponsor conducts business related to clinical research in many countries, this may involve sending your study data outside of your country. If your study data is sent to other country, your privacy will remain protected as described in this section.

- Your study data will be used by the sponsor for research purposes to support the scientific objectives of the study. The primary objectives being to further confirm the efficacy and safety of the Neuro Cochlear Implant system. In addition, data from the study may be used to improve the system and/or improve the design of future studies with the aim of maximizing performance outcomes.
- Your study data, either alone or combined with data from other studies, might be shared with your local regulatory authorities and similar government agencies from another country, as well as with the ethics review board overseeing this study.
- Study data (which does not identify you) might be published in medical journals or shared with other others as part of scientific discussion.
- To extent permitted by applicable laws, the sponsor, the ethic review board, the regulatory authority and/or other regulatory agencies in other countries, might review the original health records, which contain information that directly identifies you to verify the accuracy and completeness of the data collected during the study.

Subject to applicable laws, you will have the right to see and copy personal health information related to the study for as long as the investigator holds this information. However, you will not be able to see or copy this information until after the study has been completed.

You may withdraw your permission at any time by providing notice to the investigator. The investigator and their staff would then no longer use or share your personal information in connection with the study unless it is essential to ensure that the study is scientifically reliable. However, the sponsor would still use your study data that was collected before you withdrew your permission. In addition, a withdrawal from the study means that you would no longer able to participate in the study.

15. SOURCE OF FUNDING FOR THE STUDY

The sponsor will pay for this research study.
Depending on countries, the sponsor is paying the investigator for their work in this study.

CONSENT FORM

To take part to this study and to allow the use and disclosure of my personal health information for the purpose of the study, I must sign and date this page.

By signing this page, I confirm the following:

I give permission for my personal health information and study data to be maintained, used and shared as described in this document.

I have read the subject information and consent form and I have had time to think about whether or not I want to take part in this study.

I understand the risks, as described herein, of cochlear implant surgery.

All of my questions about the study or this form were answered to my satisfaction. If I don't understand any of the words in this form, the investigator or their staff explained them to me.

I understand that I may have other therapeutic options and/or cochlear implant device choices and have voluntarily agreed to be implanted with the Neuro Zti cochlear implant.

I voluntarily agree to take part in this study, to follow the study procedures and to provide necessary information to the investigator or its staff members as requested.

I understand that I may freely to stop being a part of this study at any time.

I have received a copy of the subject information and consent for.

By signing this consent form, I have not given up any of my legal rights.

_____ Subject's name (printed)	_____ Investigator's name (printed)
_____ Subject Signature	_____ Investigator signature
Date: |__|__|/|__|__|/|__|__|__|__|	Date: |__|__|/|__|__|/|__|__|__|__|

Appendix 3: ADVERSE EVENT REPORT FORM

ADVERSE EVENT REPORT FORM
Neuro Zti cochlear implant-system Efficacy and Safety in Adults

Study ID	
Site number	
Investigator	

Adverse event	Start date	Stop date	Severity	Relationship to the study device	Relationship to trial procedure?	Action taken	Treatment/therapy? (If yes, complete concomitant form)	Outcome of AE	Anticipated AE?	Serious Adverse Event? (If yes, complete SAE form)
1.			☐Mild ☐Moderate ☐Severe	☐ Definitely related ☐ Possible related ☐ Not related ☐ Unknown	☐ Improbable ☐ Possible ☐ Probable ☐ Certainly ☐ Unknown	☐ None ☐ Discontinued permanently ☐ Discontinued temporarily ☐ Unknown	☐ Yes ☐ No	☐ Death ☐ Not Recovered ☐ Recovered ☐ Recovered with sequelae ☐ Recovering ☐ Unknown	☐ Yes ☐ No	☐ Yes ☐ No
2.			☐Mild ☐Moderate ☐Severe	☐ Definitely related ☐ Possible related ☐ Not related ☐ Unknown	☐ Improbable ☐ Possible ☐ Probable ☐ Certainly ☐ Unknown	☐ None ☐ Discontinued permanently ☐ Discontinued temporarily ☐ Unknown	☐ Yes ☐ No	☐ Death ☐ Not Recovered ☐ Recovered ☐ Recovered with sequelae ☐ Recovering ☐ Unknown	☐ Yes ☐ No	☐ Yes ☐ No
3.			☐Mild ☐Moderate ☐Severe	☐ Definitely related ☐ Possible related ☐ Not related ☐ Unknown	☐ Improbable ☐ Possible ☐ Probable ☐ Certainly ☐ Unknown	☐ None ☐ Discontinued permanently ☐ Discontinued temporarily ☐ Unknown	☐ Yes ☐ No	☐ Death ☐ Not Recovered ☐ Recovered ☐ Recovered with sequelae ☐ Recovering ☐ Unknown	☐ Yes ☐ No	☐ Yes ☐ No
4.			☐Mild ☐Moderate ☐Severe	☐ Definitely related ☐ Possible related ☐ Not related ☐ Unknown	☐ Improbable ☐ Possible ☐ Probable ☐ Certainly ☐ Unknown	☐ None ☐ Discontinued permanently ☐ Discontinued temporarily	☐ Yes ☐ No	☐ Death ☐ Not Recovered ☐ Recovered ☐ Recovered with sequelae	☐ Yes ☐ No	☐ Yes ☐ No

Adverse event	Start date	Stop date	Severity	Relationship to the study device	Relationship to trial procedure?	Action taken	Treatment/therapy? (If yes, complete concomitant form)	Outcome of AE	Anticipated AE?	Serious Adverse Event? (If yes, complete SAE form)
						☐ Unknown		☐ Recovering ☐ Unknown		
5.			☐Mild ☐Moderate ☐Severe	☐ Definitely related ☐ Possible related ☐ Not related ☐ Unknown	☐ Improbable ☐ Possible ☐ Probable ☐ Certainly ☐ Unknown	☐ None ☐ Discontinued permanently ☐ Discontinued temporarily ☐ Unknown	☐ Yes ☐ No	☐ Death ☐ Not Recovered ☐ Recovered ☐ Recovered with sequelae ☐ Recovering ☐ Unknown	☐ Yes ☐ No	☐ Yes ☐ No
6.			☐Mild ☐Moderate ☐Severe	☐ Definitely related ☐ Possible related ☐ Not related ☐ Unknown	☐ Improbable ☐ Possible ☐ Probable ☐ Certainly ☐ Unknown	☐ None ☐ Discontinued permanently ☐ Discontinued temporarily ☐ Unknown	☐ Yes ☐ No	☐ Death ☐ Not Recovered ☐ Recovered ☐ Recovered with sequelae ☐ Recovering ☐ Unknown	☐ Yes ☐ No	☐ Yes ☐ No
7.			☐Mild ☐Moderate ☐Severe	☐ Definitely related ☐ Possible related ☐ Not related ☐ Unknown	☐ Improbable ☐ Possible ☐ Probable ☐ Certainly ☐ Unknown	☐ None ☐ Discontinued permanently ☐ Discontinued temporarily ☐ Unknown	☐ Yes ☐ No	☐ Death ☐ Not Recovered ☐ Recovered ☐ Recovered with sequelae ☐ Recovering ☐ Unknown	☐ Yes ☐ No	☐ Yes ☐ No
8.			☐Mild ☐Moderate ☐Severe	☐ Definitely related ☐ Possible related ☐ Not related ☐ Unknown	☐ Improbable ☐ Possible ☐ Probable ☐ Certainly ☐ Unknown	☐ None ☐ Discontinued permanently ☐ Discontinued temporarily ☐ Unknown	☐ Yes ☐ No	☐ Death ☐ Not Recovered ☐ Recovered ☐ Recovered with sequelae ☐ Recovering ☐ Unknown	☐ Yes ☐ No	☐ Yes ☐ No

Appendix 4: SERIOUS ADVERSE EVENT REPORT FORM

1. REPORT SEQUENCE ☐ Initial ☐ Follow-up ☐ Final

FAX to Dan GNANSIA, PhD: +00 33 4 93 95 38 01 or dagn@oticonmedical.com

2. Country where the AER occurred:_____

Center ID: |__|__|

Investigator name: _____

3. Source for clinical trial only	Protocol/study ID: _____	☐PMS/PMA RBM n° : _____

4. PATIENT DATA

Initials |__|__|__| |__|__| **patient ID** |__|__|

Gender: ☐Male ☐ Female

Date of Birth |__|__| |__|__|__| |__|__|__|__| (mm/ddd/yyyy) weight: |__|__|__|kg height: |__|__|__| cm

Date of enrolment: |__|__| |__|__|__| |__|__|__| __| (mm/ddd/yyyy)

Date of implantation: |__|__| |__|__|__| |__|__|__|__| (mm/ddd/yyyy)

Date of death: |__|__| |__|__|__| |__|__|__|__| (mm/ddd/yyyy)

5. NARRATIVE : provide clear narrative description of the sequence of events, diagnosis and any relevant details. If additional space is needed, use a Narative supplement page.

☐ Check if Narrative Supplemental page

_____

_____

_____

_____

6. REACTION DATA

Complete below reaction level characteristics for this specific adverse event

Reporter awarness date: |__|__| |__|__|__| |__|__|__|__|

Onset date/date of incidence: |__|__| |__|__|__| |__|__|__|__|

Stop date/date of incidence resolved: |__|__| |__|__|__| |__|__|__|__|

Is there a reasonable possibility the serious adverse event is related to the clinical trial procedure?

☐Yes ☐No

Adverse event description: _____

Serious criteria (check all that apply) *death is an outcome	**☐ Death*** date: |__|__||__|__|__||__|__|__|__| Cause: _____ Autopsy: ☐ Yes ☐ No Conclusion: _____	***Chek this box:*** ***if the subject died***

	☐ **Serious injury**	***Check this box:*** ***if the device SAE led to a serious deterioration in state of health.*** ***Deterioration of state of health can include: life- threatening illness or injury, permanent damage to a body structure, or a medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure.***
	☐ **Life-threatening**	**Check this box:** **If the subject was immediate risk of death from the device SAE**
	☐ **Permanent impairement/damage of the body structure/function (disability)**	***Check this box:*** ***If the subject sustained permanet impairement, damage of a body srtructure or function (disability) as a result of the device SAE.***
	☐ **Required medical surgical intervention to prevent permanent impairement/Damage to a body function/structure, specify treatement/intervention** **_____** **_____** **_____**	***Check this box:*** ***If the device SAE required medical or surgical intervention to prevent permanet impairement/damage to a body structure/function.*** ***Specify the treatment/intervention in the space provide.***
	☐ **Other, specify:** **_____** **_____** **_____**	***Check this box:*** ***If the the criteria listed above are not relevant.*** ***Specify in the space provided the seriousness criteria***
Clinical outcome **(check one box only)**	☐ **Death (if the outcome is death due to the listed SAE (ie, where "Death" is checked off in the Serious Criteria field above), leave this field blank.))** ☐ **Not recovered** ***(check Not recovered if the SAE is not only still present at the time of the report, but also the same or worse than at outset)*** ☐ **Recovered** ☐ **Recovered with sequelae** ☐ **Recovering** ***(chek Recovering if the SAE was still present but improved or better than at outset)*** ☐ **Unknown**	

Investigator Causality: **Relatedness of AE/Device Deficiency** *specify in Remarks Section	**Is there a reasonable possibility that the event is related to the device?** ☐ Yes ☐ No
	If No, what is the most likely cause? ☐ Procedure-related ☐ Disease under study ☐ Other illness* ☐ Concomitant treatment/Therapy* ☐ Other* ☐ Unknown Remarks: _____

7. Subject suspect device data

Device trade/brand name: _____ **Licence n°:** _____ ☐ Implant ☐ Processor ☐ Accessories **Labelled Sterile:** ☐ **Yes** ☐ **No** **Model n°:** _____ **Software version:** _____	**Serial n°:** _____ **Batch/lot n°:** _____
Date of implantation: |__|__| |__|__|__| |__|__|__|__| (dd/mmm/yyyy)	Date of end use: |__|__| |__|__|__| |__|__|__|__| (dd/mmm/yyyy)
Date of first use: |__|__| |__|__|__| |__|__|__|__| (dd/mmm/yyyy)	Date of explantation: |__|__| |__|__|__| |__|__|__|__| (dd/mmm/yyyy)
Device sent for the manufacturer for expertise: ☐ **Yes, date:** |__|__| |__|__|__| |__|__|__|__| ☐ **No**	

8. Event qualification			
Expectedness:	☐ Anticipated advese event	☐ Unanticipated adverse event	
9. Action taken (multiple choice is possible)	The event stopped after the taken action?	Reliationship to medical device?	Relationship to trial procedure?
☐ None ☐ Discontinued permanently ☐ Discontinued temporarily ☐ Unknown ☐ Device change (external part/accessories) ☐ Treatment/Therapy given, please complete concomittant traitement supplemental page. ☐ Revision surgery, please complete section 10.	☐ Yes ☐ No ☐ In progress ☐ N/A	☐ Definitely related ☐ Possible related ☐ Not related ☐ Unknown	☐ Improbable ☐ Possible ☐ Probable ☐ Certainly ☐ Unknown

10. Revision surgery*, please fill in the Explantation Report Form if applicable		
☐ Skin flap infection/wound complication		
☐ Implant body rejection		
☐ Implant receiver extrusion		
☐ Electrode array damaged/not put in the right place/migrate out of place		
☐ Implant failure, please attached the clinical report		

11. Suspected treatment(s), if applicable,			
Name/DCI/dose(s)/route	Date Start/Date End	Action taken with this suspected treatment	Accountability of suspected treatment
		☐ No action taken ☐ Dose decresae ☐ Discontinuation treatment ☐ Stopping treatment ☐ Requiring therapy	☐ Improbable ☐ Possible ☐ Probable ☐ Certainly ☐ Unknown
		☐ No action taken ☐ Dose decresae ☐ Discontinuation treatment ☐ Stopping treatment ☐ Requiring therapy	☐ Improbable ☐ Possible ☐ Probable ☐ Certainly ☐ Unknown

12. Additional information

Medical history, surgical history, patient therapeutic treatment (must be reported if they may have an impact on advesre events, e.g. allergy, renal insufficiency, etc.)

☐ Check if patient history supplemental page

Results of additional test/exam, precise type of test and result(s)

☐ Check if Lab data supplemental page

13. Investigator

Print Name:

_____

Contact information (address, phone, fax and e-mail): _____

_____

Authorized signature:

_____

Date: |__|__| |__|__|__| |__|__|__|__|

NARRATIVE SUPPLEMENTAL PAGE

1. Narrative

Provide a clear narrative description of the sequence of events, diagnosis and any other relevant details.

CONCOMITANT TREATMENT SUPPLEMENTAL PAGE

2. Concomitant drugs				
Drug name (trade or generic) Include all drugs taken within 2 weeks before onset of the event. Exclude drug used to treat the event.	**Therapy continuing**	**Date (or duration if dates unknown)**		**Route (e.g. oral, etc.)**
		Start (dd/mmm/yyyy)	**End (dd/mmm/yyyy)**	
	☐ Yes ☐ No ☐ Unknown			
	☐ Yes ☐ No ☐ Unknown			
	☐ Yes ☐ No ☐ Unknown			
	☐ Yes ☐ No ☐ Unknown			
	☐ Yes ☐ No ☐ Unknown			
	☐ Yes ☐ No ☐ Unknown			
	☐ Yes ☐ No ☐ Unknown			
	☐ Yes ☐ No ☐ Unknown			
	☐ Yes ☐ No ☐ Unknown			
	☐ Yes ☐ No ☐ Unknown			

PATIENT HISTORY SUPPLEMENTAL PAGE

3. Patient history

Include any other illness present at the time of onset of the event, relevant medical history and pre-existing medical conditions (e.g. allergies, previous drug reaction, alcohol/drug abuse, etc.). Specify disease entity for each drug listed in the concomitant drug supplemental page)

Disease/Syndrome (specify)	Date of Onset (dd/mmm/yyyy)	Continuing	Pertinent details Include surgical procedures and dates
		☐ Yes ☐ No ☐ Unknown	
		☐ Yes ☐ No ☐ Unknown	
		☐ Yes ☐ No ☐ Unknown	
		☐ Yes ☐ No ☐ Unknown	
		☐ Yes ☐ No ☐ Unknown	
		☐ Yes ☐ No ☐ Unknown	
		☐ Yes ☐ No ☐ Unknown	
		☐ Yes ☐ No ☐ Unknown	

LAB DATA SUPPLEMENTAL PAGE

LAB DATA TEST/EXAM FINDINGS

List **only** relevant confirmatory test results for event (including autopsy results, medical imaging results, etc.) if available, source documents are considered relevant/necessary, please attach **after** transcribing results.

Test	Test date (dd/mmm/yyyy)	Test result	Test unit	Normal low	Normal high
Comments:					
Test	Test date (dd/mmm/yyyy)	Test result	Test unit	Normal low	Normal high
Test	Test date (dd/mmm/yyyy)	Test result	Test unit	Normal low	Normal high
Test	Test date (dd/mmm/yyyy)	Test result	Test unit	Normal low	Normal high
Test	Test date (dd/mmm/yyyy)	Test result	Test unit	Normal low	Normal high
Test	Test date (dd/mmm/yyyy)	Test result	Test unit	Normal low	Normal high
Test	Test date (dd/mmm/yyyy)	Test result	Test unit	Normal low	Normal high
Test	Test date (dd/mmm/yyyy)	Test result	Test unit	Normal low	Normal high
Test	Test date (dd/mmm/yyyy)	Test result	Test unit	Normal low	Normal high

Appendix 5: EXPLANTATION REPORT FORM

The implantable device could be explanted for technical or medical issues.

This explantation report form should be completed with a clinical support from Oticon Medical Neurelec and sent to Oticon Medical Neurelec whether the internal part is removed or remains in situ.

Date of filing: |__|__|/|__|__|__|/|__|__|__|__|

SOURCE OF THE INCIDENT

	Please describe
☐ Device failure	_____ _____ _____ _____ _____
☐ Medical reason	_____ _____ _____ _____ _____
☐ Other	_____ _____ _____ _____ _____

Oticon Medical representative contacted prior explantation:	☐ Yes	☐ No, comment:_____

PATIENT INFORMATION & IMPLANT INFORMATION

Center ID	
Subject ID	
Implantation date	
Explantation date	
Explanted device model	☐Neuro Zti^{CLA} ☐NeuroZTI^{EVO}
Explanted device serial number	
Sound processor serial number	

CLINICAL REPORT

Incident onset date: |__|__|/|__|__|__|/|__|__|__|__|

Incident report:

Medical reason which could be linked to the incident:

EABR testing performed	☐ Yes		☐ No
If yes, did Oticon Medical determine that device failed prior explantation	☐ Yes	☐ No	☐ Inconclusive

Integrity testing performed	☐ Yes		☐ No
If yes, did Oticon Medical determine that device failed prior explantation	☐ Yes	☐ No	☐ Inconclusive

Please document that the following has taken place:

☐	SAE reporting form completed and sent to Oticon Medical
☐	Vigilance report completed and sent to Oticon Medical
☐	Vigilance report completed and sent to local competent authority
☐	Other, please specify: _____

Please document the medical reason for device explant (*multiple choice is possible*)

☐	Performance issue
☐	Electrode migration
☐	Electrode array misplacement

☐	Implant migration/extrusion
☐	Facial nerve stimulation
☐	Shocking with device ON/OFF (*please delete as appropriate*)
☐	Pain and/or discomfort with device ON Precise location (e.g. over implant stimulator, ear canal, neck, etc.): _____ _____
☐	Pain and/or discomfort with device OFF Precise location (e.g. scalp, flap, incision line, ear canal, neck, etc.): _____ _____

SURGICAL OBSERVATIONS during device explant

Any physical signs of device failure prior explant?

☐ Yes, please describe: _____

_____

☐ No

Electrode status, did the electrode array appear to have moved since initial placement?

☐ Yes, please describe: _____

_____

☐ No

Any evidence of infection or tissue reaction?

☐ Yes, please describe: _____

_____

☐ No

Was a device re-implanted?

☐ Yes, please precise, model and serial number: _____

_____

☐ No

If yes, please describe the surgical placement of the second device

☐	Similar to placement of the first device
☐	Insertion with some resistance
☐	Partial / full insertion

☐	Other: _____ _____ _____

Explanted device returned to Oticon Medical?

☐ Yes

☐ No, please explain: _____

_____

Investigator Authorized signature: _____ Print name: _____ Date: |__|__| |__|__|__| |__|__|__|__|

Appendix 6: CLINICAL SUPPORT ROLE

0. Purpose

This document describes the function and duties of the clinical support in this clinical trial. The main task of the clinical trial support is to make sure that medial team are properly used the Neuro cochlear implant system. The clinical trial support is an Oticon Medical employee, he/she have a background in audiology, speech therapy, PhD or engineer in audiology.

1. Scope

This document applies to the clinical trial which will be conducted in Canada and Denmark to support the PMA-FDA submission.

2. References

- Neurelec Clinical Support procedure (PG0005)

3. Abbreviation

eCAP: electrical Evoked Compound Action Potential

OR: Operating Room

4. Basic role of the clinical support

The clinical support provide clinical, expertise and support to Oticon Medical's participants' centers.

Provide clinical support, information and advice to clinical teams on topics such as surgery, and post-implantation management. Also, assist with clinical trial and research studies on Oticon Medical products.

The role focus on providing clinical expertise on product, support initial stimulation, assist with clinical problems, as well as performing training to build clinical capability through clinical investigation sites.

Cochlear implant centers must have the highest quality clinical and technical support available from the manufacturer.

5. Function and duties of technical support in this clinical trial

- Represents Oticon Medical during surgeries and cochlear implants by providing all necessary advice and support.
- Support the audiologist or its representative in conducting the objective measures (impedance and ECAPs) in the OR.
- Undertake eCAP and impedance measures in OR if there is nobody from the medical team dedicated for this task.
- Supervise eCAP and impedance measure in clinic.

- Evaluate the external, internal part or accessories for a better subject management.
- Provide expertise in all aspects of implant and troubleshooting techniques.
- Provides on-call support as needed for surgeries, reprogramming, troubleshooting, and follow-up on all visits.
- Support the audiologist or its representative in device fittings especially for the first one. The following fittings could be supervise by the clinical support at the request of the investigator site.
- Troubleshoot by testing and reprogramming device integrity testing and communicate the results to the managing audiologist.

6. Education support in this clinical trial

- Educates and train surgeon and hospital team (hearing aid specialist, speech-pathologist, technician or audiologist) on technical matters relating to the cochlear implant system by conducting or coordinating:
    - One on one training session
    - In-service education programs
- Help audiologist in patient fittings
- Provide advice in and guidance to audiologist

7. What the clinical support Does Not Do in this clinical trial

- Will never been alone with the patient, the patient is supported by the medical team involved in this clinical trial.
- Does not provides audiological assessment of patient
- Does not provides “switch-on” device programming of the recipient following surgery. The audiologist switch-on the device and the clinical support advice and guide the audiologist in the fittings.
- Does not provides routine ongoing device programming
- Does not carry out evaluation of candidate outcomes
- Does not undertake eCAP or impedance measures in clinic
- Does not interfere in management of recipient device repairs
- Does not interfere in management of recipient device accessories
- Does not interfere in equipment and products required for the device implant
- Does not provide recommendation about cochlear implant candidacy following assessment

Appendix 7: PATIENT HINT PERFORMANCE

Preoperative evaluation

a) If the patient has a poor speech understanding in HINT-Q during the training (i.e. score of 0), it is recommended to performed the entire training list.

   If the patient have a poor speech understanding in HINT-Q during the evaluation with a score of 0 words correctly repeated on the first six sentences:
   - Stop the evaluation in Quiet
   - Don't conduct the evaluation in Noise
   - Record in the eCRF:
     - HINT-Q raw score =0 , % correct = 0 and percent correct=0 for the 2 lists
     - HINT-N raw score =0 , % correct = 0 and percent correct=0 for the 2 lists

b) If the patient has a proper speech understanding in HINT-Q during the training, **AND**,

   the patient has a poor speech understanding during the evaluation with a score of 0 words correctly repeated on six consecutive sentences:
   - Give a short break to the patient, and when it's time, carry on with the evaluation
   - If the score still remains at 0 in the next 3 consecutive sentences, stop the evaluation.
   - Record in the eCRF the score of 0 in the respective input fields

Postoperative evaluation

Please, see above

Appendix 8: POST-OPERATIVE ECAP MEASUREMENT

When performing post-operative ECAP measurements, follow the guidelines/recommendations below:

As a minimum, perform ECAP on one electrode (electrode 18)
If possible, perform ECAP on four electrodes (electrode 3, 8, 13, 18)

Neuro ECAP

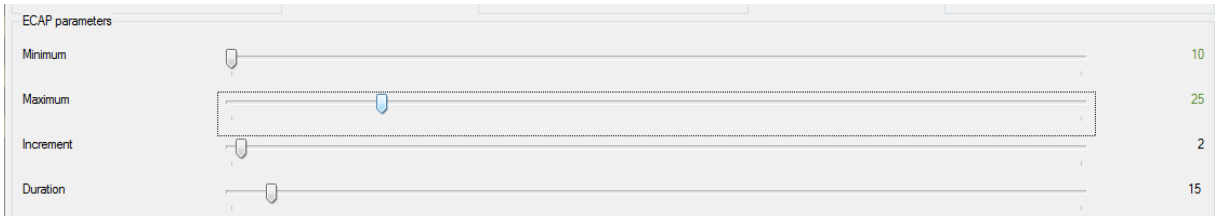
The Neuro ECAP 1.0® function allows to measure the electrophysiological responses of the auditory nerve by scanning with a range of Amplitude, for a fixed stimulation duration several electrodes.

Two modes are available:
Basic: where you can select the number of electrode to stimulate, the repetition frequency and the ECAP parameters (Minimum: Minimum Amplitude of the range tested, Maximum: Maximum Amplitude and Duration: Pulse Duration)
Advanced: where you can also choose the increment in the range of Amplitude tested, the stimulation and collection electrodes and the Number of repetitions for the measures.

Attention: Before setting the ECAP parameters during a post op. measurement, be sure to be lower than the C level of the patient.

If C levels are below 30 µs
You should respect the following rule: C levels (perceived by the patient) are defined by an amplitude A and a duration T.
Then post op ECAP should have the following parameters:
Min 10
Max= A+5
Increment=2
Duration= T-10 µs

For example, if patient is describing a sound as comfortable in a fitting window with an amplitude A of 20 and C of 25µs, then ECAP research on the corresponding electrode should be the following graph:

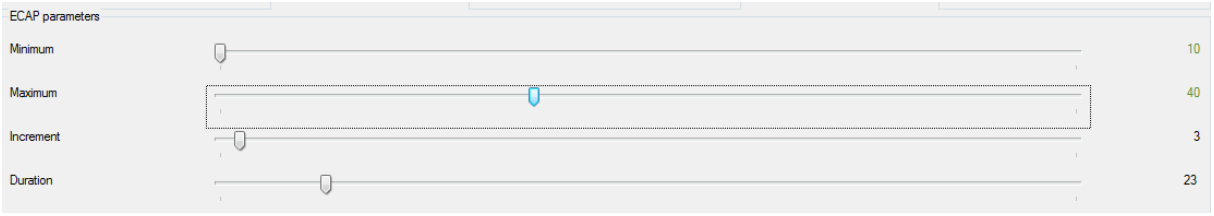


Depending on the patient perception, it is possible to go higher than those values or to stop the stimulation prior to that if auditory perception is too loud.

If C levels are above 30 µs
You should respect the following rule: C levels (perceived by the patient) are defined by an amplitude A and a duration T.
Then post op ECAP should have the following parameters:
Min 10
Max= T - 5
Increment=3
Duration= A

Note : Max should not exceed 70 CU.

For example, , if patient is describing a sound as comfortable on electrode 18 in a fitting window with an amplitude A of 23 and C of 45µs, then ECAP research parameters on the corresponding electrode should be the following graph:



On a general point of view, this post op ECAP protocol is meant to provide recommendations, the audiologist has a crucial role in the post op ECAP recording procedure as if the patient is describing a loud auditory sensation and the measurement is still running, then it is important to stop the recording to prevent the patient from receiving a too loud auditory sensation.
On the other side, if the patient is perceiving an auditory sensation that is considered as soft even at the MAX value, then the audiologist could decide to increase the MAX value.

Appendix 9: Calibration considerations

0. Purpose

This document discusses the calibration procedure for audiological assessments, taking into consideration audiological guidelines, as well as speech tests assessment tools calibration possibilities.

1. Scope

This document applies to the clinical trial which will be conducted in Canada and Denmark to support the PMA-FDA submission.

2. References

American National Standard Specification for Sound Level Meters. ANSI S1.4-1983 (R2006)/ANSI S1.4a-1985 (R2006), American National Standards Institute.

Firszt, J. B., & Holden, L. K., Skinner, W., Tobey, E., Peterson, A., & Gaggl, W., et al. (2004). Recognition of speech presented at soft to loud levels by adult cochlear implant recipients of three cochlear implant systems. Ear Hear, 25(4), 375-87.

HINT Pro 7.2 Audiometric system Operating instructions, Bio-logics Systems Corp.

IEC 61672-1:2013 Electroacoustics - Sound level meters - Part 1: Specifications. IEC. 2013

Raman G, Lee J, Chung Met al., authors; Sen S, editor. Effectiveness of Cochlear Implants in Adults with Sensorineural Hearing Loss. Rockville (MD): Agency for Healthcare Research and Quality (US); 2011 Jun 17. Available from: https://www.ncbi.nlm.nih.gov/books/NBK285762/

Westhorp Sue, "Decibel scales in audiology." BATOD Magazine November 2009: pages 11- 12. Web. URL: http://www.batod.org.uk/content/resources/audiology/refreshers/general/G3-decibels.pdf

Zwolan, T., Thomas, E. Contemporary Protocols for Evaluating Cochlear Implant Candidacy of Children. Perspectives on Hearing and Hearing Disorders in Childhood 19(1):4-13 · March 2009 DOI: 10.1044/hhdc19.1.4

3. Abbreviations

dB SPL: Decibel Sound Pressure Level

dBA: Decibel with A-weighted correction

HINT: Hearing In Noise Test

4. Recommendations and guidelines

In the clinical protocol "Neuro Zti cochlear implant-system Efficacy and Safety in Adult", efficacy is assessed using HINT sentences tests presented at 60dB SPL. This presentation level has been

chosen in accordance with previous literature reporting HINT results in adult and children with cochlear implant, where presentation levels were expressed in dB SPL (e.g. Firszt et al., 2004; Zwolan & Thomas, 2009), and it is also consistent with American technology assessment report on the effectiveness of cochlear implants in adults (Raman et. al., 2011). Moreover, 60dB SPL is also a presentation level chosen for cochlear implant candidacy preoperative testing (Firszt et al., 2004).

HINT sentences in quiet at 60 dB SPL is therefore a relevant speech test to assess cochlear implant effectiveness, with comparison of preoperative and postoperative scores.

5. Calibration of speech test software tool in dBA

HINT speech tests are conducted with the help of a dedicated software that facilitates sentences presentation at controlled level and recording of patient's responses. Depending on language, either HINT Pro software of an in-house replica is used.

These tools are calibrated in dBA, and do not use the dB SPL scale for presentation levels (see HINT Pro Operating Instructions). The dBA scale reflects the sensitivity of the human ear at different frequencies and it is used for measures of sound field assessments (Westhorp, 2009).

The dBA scale is the most commonly used one among those defined in the International standard IEC 61672:2003 and in other standards on sound level measurement like ANSI standard ANSI S1.4-1981 (R2006). This scale is applied in order to account for the relative loudness perceived by the human ear, known to be less sensitive to lower frequencies.

6. The dB SPL sound scale and differences with dBA

The dB SPL scale refers to physical sound pressure level of the physical acoustic vibration. This scale is used to measure sound levels evoked by vibrations of physical objects (vibrating plates, membranes…), it is therefore widely used to describe microphones and loudspeakers acoustic characteristics. In auditory science, dB SPL may refer to hearing aid (Westhorp, 2009) or cochlear implant microphone characteristics as a measure of acoustic sensitivity of the device.

The dB SPL and dBA scale therefore differ, especially at low frequencies. Below is a table (adapted from Westhorp, 2009) with conversion values at different frequencies.

Converting dBA to dB SPL				
250 Hz	500 Hz	1000 Hz	2000 Hz	40000 Hz
+5 dB	-6 dB	-3 dB	-1 dB	-1 dB

According to this table, for a spectrally flat white noise, mean difference between dBA and dB SPL is -6dB on average across frequencies. For a speech signal, known to carry richer information at low frequencies, this difference will be less than 5dB on average across frequencies.

7. Conclusions

Audiological recommendations suggest 60 dB SPL presentation level for cochlear implant assessment of performance. Speech test tools do not offer the possibility to calibrate presentation levels in dB SPL but rather in dBA, consistently with sound perception of speech. The comparison of the 2 scales shows differences lower than 5dB for speech, and is considered limited.

Therefore, for the study “Neuro Zti cochlear implant-system Efficacy and Safety in Adult”, all HINT tests are conducted at 60 dBA, in all participating centers in all countries, and for all evaluations.

This document discusses the calibration procedure for audiological assessments, taking into consideration audiological guidelines, as well as speech tests assessment tools calibration possibilities.

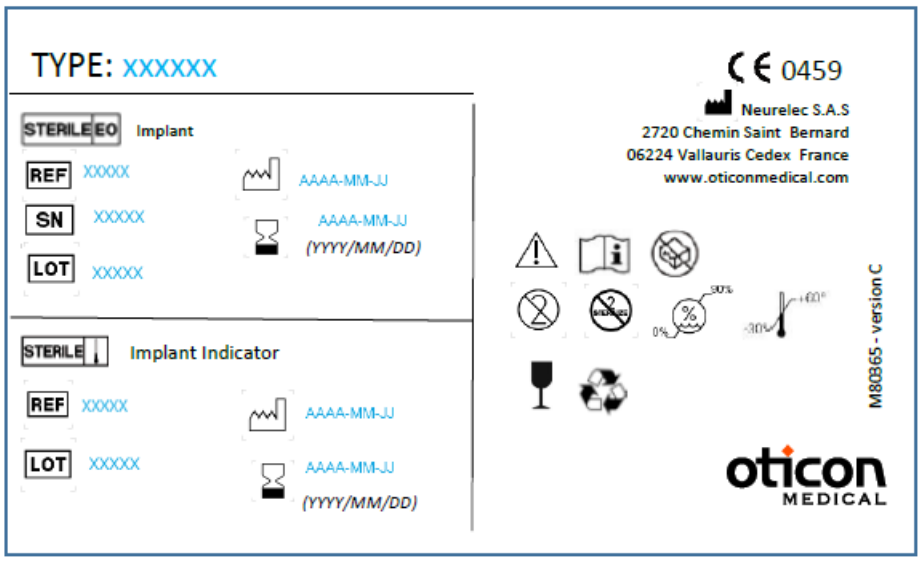
Appendix 10: DEVICE LABELING

The packaging of device will be stamped with the self-adhesive label with the statement “ONLY FOR CLINICAL TRIAL”.

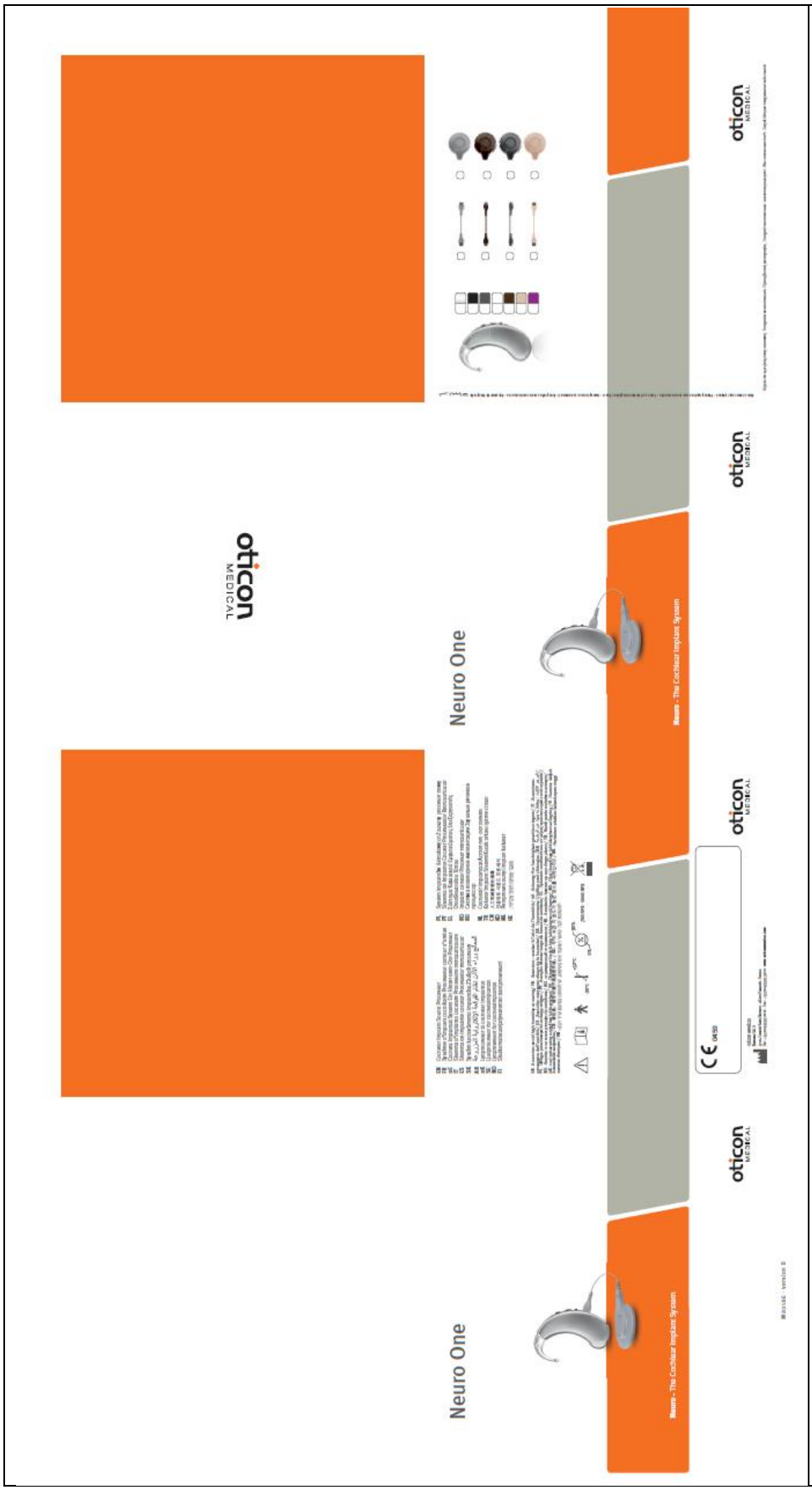
Self-adhesive label

Neuro Zti cochlear implant
Outer pack & outer pack label

Oticon Medical
Neurelec S.A.S
272 o Chemin Saint Bernard
062 20 Vallauris – France
TEL: +33 (0)4 93 95 18 18
FAX: +33 (0)4 93 95 38 01
in fo@oticonmedical.com



Neuro One sound processor
Outer pack & outer pack label


oticon
MEDICAL
Neuro One
Neuro - The Cochlear Implant System
oticon
MEDICAL
Neuro One
Neuro - The Cochlear Implant System
oticon
MEDICAL
oticon
MEDICAL
oticon
MEDICAL
oticon
MEDICAL
DESIGNATION
REF
Code article
SN
N° de série
AAAA-MM-JJ
CODE BARRE
DATA MATRIX
M80260-Version B

Appendix 11: DECLARATION OF HELSINKI

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the: 29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington, DC, USA, October 2002 (Note of Clarification added) 55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study. Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a nonvulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed.

The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions. Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent 25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative.

If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available