SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Cochlear Implant System

Device Trade Name: Neuro Cochlear Implant System

Device Procode: MCM

Applicant's Name and Address: Oticon Medical
2720 Chemin de Saint Bernard
06220 Vallauris
FRANCE

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P200021

Date of FDA Notice of Approval: June 23, 2021

II. INDICATIONS FOR USE

The Neuro Cochlear Implant System (NCIS) is indicated for individuals eighteen (18) years of age or older, with bilateral severe-to-profound sensorineural hearing loss, who obtain limited benefit from appropriately fitted hearing aid(s).

Severe-to-profound hearing loss is determined by a pure-tone average (PTA) superior or equal (≥) to 70 dB HL at 500, 1000 and 2000 Hz. Limited benefit from amplification is defined by scores of 50% or less on Hearing in Noise Test (HINT) sentences in quiet or noise, in the best-aided listening condition. Unless already appropriately fitted with hearing aids, it is recommended that candidates undergo a hearing aid trial period of three (3) months.

III. CONTRAINDICATIONS

The NCIS is not indicated in the following conditions:

- Absence of cochlear or auditory nerve development.
- Hearing loss due to lesions of acoustic nerve or central auditory pathway.
- Anatomic abnormalities, bone growth or fibrosis preventing the placement of the chosen electrode array inside the cochlea.
- Active external or middle ear infections or tympanic membrane perforation in the ear to-be- implanted.
- Presence of medical contraindications to middle-ear or inner-ear surgery or anesthesia, as required.
- Psychological instability or unrealistic expectations regarding benefits.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Neuro Cochlear Implant labeling.

V. DEVICE DESCRIPTION

A. General Description

The Neuro Cochlear Implant System (NCIS) is composed of external and internal components (**Figure 1**). The external components include the Neuro 2 Sound Processor (Neuro 2 SP), a headpiece antenna, and connecting cable. The internal components include the implantable Neuro Zti receiver/stimulator (Neuro Zti) and an electrode array (CLASSIC or EVO). The NCIS is programmed for individual patients using the Genie Medical CI Fitting Software (GMCI) installed on the programming site's personal computer, and the CI Link Fitting interface (CI-Link).

Figure 1: Overview of the NCIS

Left: Neuro 2 Sound Processor alone (without headpiece antenna and connecting cable).Middle and right: Two views of the Neuro 2 Sound Processor, headpiece antenna, and Neuro Zti implant.

B. Neuro 2 Sound Processor

The Neuro 2 Sound Processor captures and processes sound. It provides power and data to the Neuro Zti via an inductive link. The electrical components are housed within a mechanical design that enables the patient to wear the Neuro 2 Sound Processor behind the ear (**Figure 2**). It is powered by two Zinc-air batteries or by a rechargeable Lithium-ion battery (small and large options). During a cochlear implant fitting it is powered directly by the fitting interface (CI-Link).

Figure 2: Illustration of the Neuro 2 Sound Processor including its Headpiece Antenna and Connecting Cable

Two omnidirectional microphones located at the top of the Neuro 2 Sound Processor capture the incoming sound signal. The Neuro 2 Sound Processor can also receive audio input through a telecoil and through an induction-loop system. The telecoil enables listening in public places equipped with a specific telecoil transmitter. The induction-loop system uses an off-the-shelf external Streamer that allows sound input from audio devices (e.g., mobile phone, television, MP3 player) to be sent to the sound processor.

The headpiece antenna is connected to the Neuro 2 Sound Processor via a replaceable cable. The headpiece antenna includes a magnet for retention and a coil to enable an inductive link for power and communication with the implanted Neuro Zti. There are two antennas provided to ensure optimal power transfer to the internal device, a short distance (SD) antenna for thin skin flaps and a long distance (LD) antenna for thick skin flaps. Headpiece magnets with different strengths may be used to optimize the retention force.

C. Neuro Zti Implant

The Neuro Zti is defined as a single cochlear implant receiver/stimulator plus electrode array. **Figure 3** depicts the Neuro Zti from the top, side, and bottom views. The electrical components of the receiver/stimulator are hermetically encased within a mechanical zirconia/titanium housing that is overmolded with medical grade silicon. This housing is connected to a 20-contact electrode array with an integrated reference electrode located on the lead close to the receiver/stimulator. The feedthroughs in the housing enable electrically insulated connections between the internal electronics and the electrode array. The Neuro Zti offers bidirectional telemetry. Forward telemetry facilitates electrical stimulation of the cochlea. Backward telemetry is capable of providing information from the receiver to the external components and/or clinical fitting software.

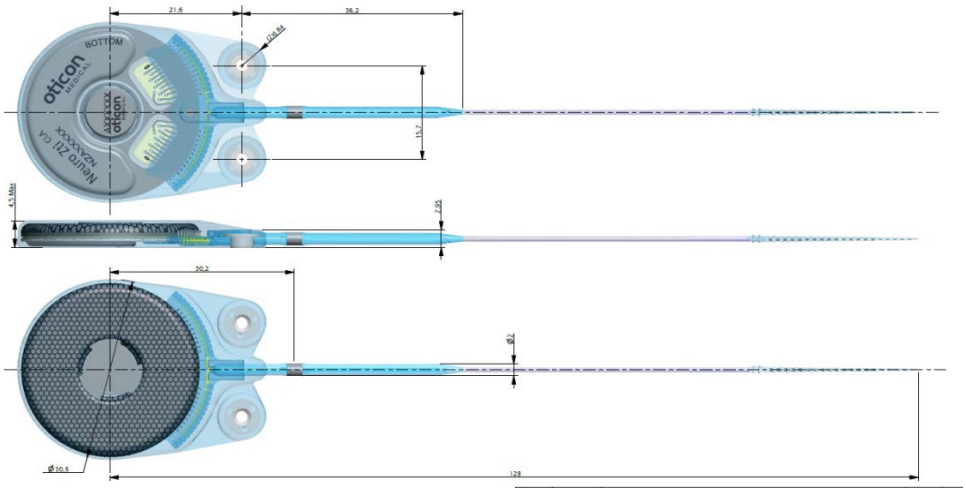

Figure 3: Diagram of the Neuro Zti Receiver/Stimulator Showing Dimensions in mm

The Neuro Zti receiver/stimulator is designed to be placed surgically under the periosteum on the temporal side of the skull behind the pinna. There are two unique features that differentiate the design from receiver/stimulators approved by FDA to date. The first is an integrated fixation system that uses two self-tapping screws for fixation to the skull. There are two titanium inserts that are part of the receiver/stimulator case through which each screw is placed to ensure that a maximum penetration depth is not exceeded. Second, an opening in the middle of the stimulator holds a surgically removable/replaceable magnet to facilitate magnetic resonance imaging (MRI), if required.

The Neuro Zti communicates with the Neuro 2 Sound Processor via an inductive link facilitated by two parallel coils located in the receiver/stimulator and in the external antenna. The mechanical stability of the link is maintained by magnets located in the center of the two coils.

D. Electrode Arrays

The Neuro Zti can be configured with two different electrode arrays, the CLASSIC and the EVO. The configuration with the CLASSIC array is called the Neuro Zti^{CLA}. The configuration with the EVO electrode array is named the

Neuro Zti^{EVO}. The main difference between the two electrode arrays is that the EVO has a slightly smaller form factor than the CLASSIC, and therefore is less stiff (**Figure 4**). Electrode selection and insertion technique are left up to the surgeon depending upon the anatomical condition of the patient's cochlea.

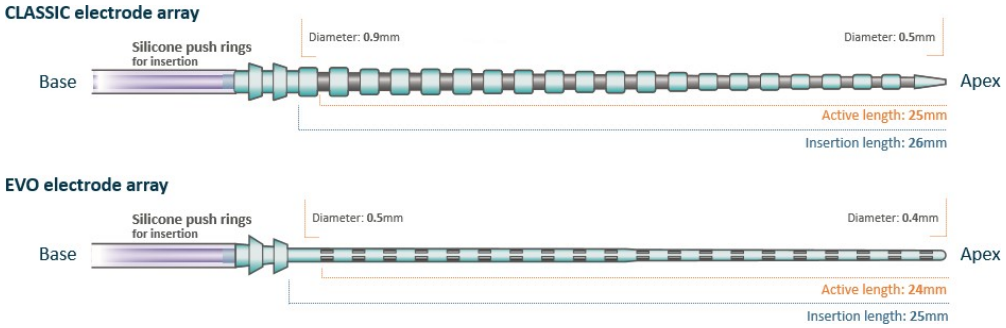

Figure 4: CLASSIC and EVO Electrode Arrays

E. Stimulation Circuitry & Methodology

The stimulation mode used in the NCIS combines all non-stimulating intracochlear electrodes and one extracochlear reference electrode as return electrodes by turning them into a ground state. Such a stimulation mode keeps the power consumption low as no current source is needed to drive return electrodes. The average percentage of return current shared by intracochlear electrodes is 80%, with the last 20% returning to the extracochlear reference electrode. The combination of intra- and extracochlear return electrodes permits stimulation while mitigating fitting threshold variability observed in stimulation modes using only intracochlear return electrodes (*e.g.*, partial-Tripolar mode vs. Tripolar mode [1]).

The stimulation mode of the NCIS then affects the pulse waveform, as the return electrodes are not actively participating in the pulse shape by delivering anodic or cathodic stimulation. Therefore, at the stimulating electrode level, implant power is required only in the first phase of stimulation (anodic) while the current is returning to all non-stimulating grounded electrodes. In the second, non-stimulating (cathodic) phase, the stimulating electrode with its capacitor in series is connected to ground. This provides a charge balancing effect which follows an exponential decay profile.

Following clinical and worst-case scenarios, all safety aspects of the stimulation associated with the electrical pulse shape, maximum charge and charge density, leakage or balance between anodic and cathodic phases were compared, evaluated, and validated from computational models and direct implant tests. In addition, the long-term effect of this stimulation methodology on electrode contacts integrity was analyzed from explanted legacy cochlear implant systems using similar stimulation.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of severe-to-profound sensorineural hearing loss. The alternative treatments include the acquisition of augmentative and alternative communication skills, including sign language or lip-reading. These practices do not involve surgery and the risks associated to a surgical procedure. Their benefits can, however, be limited as sign language can be shared only with persons who understand this form of communication and lip-reading requires that the speaker is facing the reader and that vision and lighting conditions are favorable. Conventional hearing aids can be used as alternative devices that do not require a surgical procedure and therefore avoid the risk associated with a surgical procedure. Patients are proposed to receive a cochlear implant system only if they show limited benefit from appropriately fitted, conventional hearing aids. Finally, (non-surgical) vibrotactile systems or other augmented reality systems can be used. However, they do not allow patients to achieve the ranges of speech recognition levels comparable with those achieved by cochlear implant systems. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the treatment option that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The NCIS is the fourth-generation implant system developed by Oticon Medical. Prior to 2013, the devices were marketed with established safety and effectiveness by Neurelec in Canada and Europe. Since 2013, they have been marketed by Oticon Medical.

The NCIS is approved for marketing in the following countries: Algeria, Argentina, Australia, Austria, Belgium, Brazil, Cameroon, Canada, Chile, Colombia, Denmark, Egypt, Finland, France, Gabon, Germany, Greece,

Hungary, Ireland, Israel, Italy, Lebanon, Lithuania, Malaysia, Morocco, Myanmar, Netherlands, New Zealand, Norway, Oman, Pakistan, Peru, Poland, Portugal, Romania, Saudi Arabia, Senegal, South Korea, Spain, Sweden, Switzerland, Thailand, Turkey, United Arab Emirates, Ukraine, United Kingdom, and Uzbekistan.

The device has not been withdrawn from any (international) market.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the NCIS.

Risks related to the surgery:

- Normal risks associated with surgery and general anesthesia; risks increase in some patients with certain medical conditions.

- Complications associated with the surgical procedure, such as skin irritation, infection, meningitis inflammation*, epidural or subdural hematoma, pain, swelling, wound healing complications, CSF leakage, perilymphatic fistula, facial nerve injury leading to transient or permanent facial nerve paralysis.

***Meningitis**

It is important to consider the risk of meningitis. Meningitis can occur in rare cases, but can result in serious illness. Before cochlear implantation, patients should be appropriately counselled regarding this risk.

Meningitis vaccine is strongly recommended, as it can reduce the risk of developing meningitis. Physicians should provide adequate counselling regarding this risk and review the candidate's vaccination records or verify their immunization status prior to considering implantation. Vaccination recommendations are available on the Center for Disease Control and Prevention website, www.cdc.gov.

Risks related to the implant:

- Once the implant is in place, the risk of revision surgery or device explantation still exists in case of device failure, decrease of device or for medical reasons.
- Loss of residual hearing associated with the electrode array insertion.
- Transient vertigo or dizziness, persistent pain or discomfort, numbness, transient or permanent taste disturbance.
- Induction of tinnitus.
- Aggravation of pre-existing tinnitus.
- Stimulation of facial nerve.
- Unusual pain.
- Perception of uncomfortable sound sensations can lead to a reduction in the number of active electrodes.
- Device may result in uncomfortable, intermittent or non-auditory sensations.
- Electrode array misplacement, magnet displacement.
- Screw migration, electrode array migration, receivermigration.
- Receiver extrusion, electrode array extrusion, magnet extrusion.
- Implant rejection, foreign-body reaction or allergic reaction to medical grade silicone, platinum- iridium, or titanium.

Risks related to the sound processor:

Wearing the sound processor might in some rare cases lead to:

- Discomfort, pain, skin redness, skin irritation, or sore pinna.
- Painful pressure or heating sensation under the antenna magnet.
- Intermittent headaches.
- Reverberation at activation.

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

The NCIS underwent non-clinical mechanical, electrical, functional, biocompatibility, sterilization validation, packaging validation, shelf-life validation, and bacterial endotoxin testing to support the proposed intended use.

A. Laboratory Studies

The table below summarizes the laboratory studies performed on **Neuro ZTI Implants**.

Test	Purpose	Acceptance Criteria	Results
Useful life	Demonstrate that the cochlear implant intended useful life is 10 years. Testing per ANSI AAMI CI86 Section 6.2	Electrical performance: No degradation of performance Mechanical performance: No degradation of performance	**PASS**
Test	**Purpose**	**Acceptance Criteria**	**Results**
Mechanical Testing			
Immunity to Vibration Stresses during Normal Use and Handling	To evaluate Neuro Zti implant integrity after vibration tests. Testing per ANSI AAMI CI86 Section 23.1.1.	Visual performance, electrical functions verified, no leak and extraction magnet strength value verified	After vibration testing: – Visual performance: no degradation of visual performance. – Electrical function is maintained. – Hermeticity of implant is maintained. – Removable magnet function is maintained

Immunity to Minor Mechanical Impact Stresses during Implantation Handling	To evaluate Neuro Zti implant integrity after minor shock tests. Testing per ANSI AAMI CI86 Section 23.1.2.	Visual performance, electrical functions verified, no leak and extraction magnet strength value verified	After minor shock testing: – Visual performance: no degradation of visual performance. – Electrical function is maintained. – Hermeticity of implant is maintained. – Removable magnet function is maintained.
Immunity to Mechanical Impact Stresses during Normal Use, including Trauma	To evaluate Neuro Zti implant impact resistance. Testing per ANSI AAMI CI86 Section 23.1.3.	Visual performance, electrical functions verified, no leak and extraction magnet strength value verified, moisture limit verified	After impact testing: – Electrical function is maintained. – Hermeticity of the implant is maintained. – Removable magnet function is maintained. – Moisture limit is maintained.
Immunity of Implantable Leads to Tensile Forces	To evaluate the integrity of the implantable leads of the Neuro Zti implant after tensile forces testing. Testing per ANSI AAMI CI86 Section 23.1.6.	No breakage in the wires or welds, no silicone tears, no ungluing of components, lead electrical insulation test verified and resistance measurement verified. Acceptance criteria is ≥12 functional electrodes with no contiguous failed electrodes.	After Tensile testing of the electrode array: – There is no breakage in the wires or welds, no silicone tears, no ungluing of components. – Electrical function is maintained.
Device Immunity to Stresses Caused by Atmospheric Pressure Changes	To evaluate the Neuro Zti implant integrity after atmospheric pressure changes tests. Testing per ANSI AAMI CI86 Section 24.1	Visual performance, electrical functions verified, no leak	After pressure testing: – Visual performance: no degradation of visual performance. – Electrical function is maintained. – Hermeticity of implant is maintained.

Stress Relief of Junctions in Implantable Leads	To evaluate the resistance to stress of the junctions of the implantable leads of the Neuro Zti Implant. Testing per ANSI AAMI CI86 Section 23.1.7.	No breakage in the wires or welds, no silicone tears, no ungluing of components, insulation test verified, and resistance measurement verified	After stress relief of junction testing: – There was no breakage of wires or welds, no infiltration of saline solution, no detachment or ungluing of components, and no silicone tears. – Electrical function is maintained.
Hermeticity testing and compliance	To evaluate the Neuro Zti implant casing hermeticity. Testing per ANSI AAMI CI86 Section 20.6	For the fine leak test, the device leak rate shall not exceed 5 x 10^{-9} Pa m^3/s. For the gross leak test, no definite stream of bubbles or two or more large bubbles shall not originate from the same point of the stimulator case.	All samples are hermetic.
Implantable device internal moisture content	To quantitatively measure the relative concentration of the internal vapor content, including water vapor, in hermetically sealed, gas filled microelectronic devices using a mass spectrometric technique Testing per ANSI AAMI CI86 Section 20.7	Moisture limit equivalent or under 5000 ppm	All samples are under the limit of 5,000 ppm.
Immunity of Implantable Leads to Flexural Stresses	To evaluate the integrity of the electrode array (implantable leads) of the Neuro Zti implant after flexion testing. Testing per ANSI AAMI CI86 Section 23.1.8.	No breakage in the wires or welds, no silicone tears, no ungluing of components, insulation test and resistance measurement verified. Acceptance criterion is ≥12 functional electrodes with no contiguous failed electrodes.	After flexion testing of the electrode array: - There is no breakage of the wires or welds, no silicone tears, no ungluing of components. - Electrical function is maintained.

Magnetic Resonance Imaging Compatibility			
Test	**Purpose**	**Acceptance Criteria**	**Results**
Torque	To measure the torque that may be induced by the static magnetic field (B0) on the device. Testing per ASTM F2213-06	Magnetically induced torque shall be less than the worst-case gravity-induced torque, which is defined as the product of the weight of the device and the longest linear dimension (3.46 ± 0.01 mN.m).	Even though the maximum torque exceeds the standard limit, there is no risk for patients.
Magnet Flipping Out	To assess the ability of the cochlear implant magnet to remain in place when exposed to the strong static magnetic field (B0). Testing per ASTM F2213-06	No risk to the patient due to magnet flipping out of pocket is acceptable.	The conclusion of the test report showed that there is no magnet movement.
Displacement Force	To measure the displacement force that may be induced by an MRI static magnetic field (B0) on the device. Testing per ASTM F2052-15	Magnetically induced force shall be less than the force on the device due to gravity (its weight) 113 ± 7 mN.	Even though the maximum force exceeds the standard limit, there is no risk for patients.
Gradient Induced Vibration	To evaluate the impact of gradient induced vibration on the device due to interaction between the gradient- induced eddy current magnetic moments of the device and the static magnetic field (B0). Testing per ISO/TS 10794 clause 10	Unacceptable risk to the patient.	No device malfunction has been reported and no risk for patients has been identified.

Radio Frequency Induced Heating	To determine a conservative upper bound of the maximum temperature increase in the vicinity of the device caused by the radio-frequency (RF) fields. Testing per ISO/TS 10794 clause 8	The radio-frequency-induced heating shall not exceed a 2°C change	This temperature increase has been considered safe for patients.
Gradient Induced Heating	To measure the gradient induced heating of the device due to switching magnetic field which generate eddy current in metallic material. Testing per ISO/TS 10794 clause 9	The gradient-induced heating shall not exceed a 2°C change	The maximum temperature rise detected on the device was below the maximum acceptable temperature rise.
RF Unintentional Device Output	To evaluate the Radio Frequency (RF)-induced malfunction and RF rectification of the device. Testing per ISO/TS 10794 clause 15	The unintentional output remains within the safe stimulation charge limits	No device malfunction has been reported and no risk for patients has been identified.
Gradient Unintentional Device Output	To measure the gradient induced extrinsic electrical potentials on the device due to gradient magnetic field exposure. Testing per ISO/TS 10794 clause 13	The unintentional output remains within the safe stimulation charge limits	The maximum measured value for the Leakage Test has been considered as safe for patients.
Implant Magnet Weakening	To characterize the demagnetization of the implant magnet when exposed to strong MR scanner static magnetic field (B0). Testing per ANSI AAMI CI 86 Section 21.7	The implant magnet shall not weaken during MRI scanning to an extent that does not allow sufficient attraction of the external coil to the implant. Magnet polarity reversal is acceptable, provided that the external headpiece can remain attached.	**PASS**

Combined field malfunction	To evaluate device malfunction when exposed to a combined field (simultaneous exposure to the static magnetic field (B0), gradients magnetic field and RF conditions). Testing per ISO/TS 10794 clause 17	The functionality of the device shall not be affected under test conditions.	No device malfunction has been reported.
Gradient Induced Malfunction	To evaluate the gradient-induced malfunction (caused by the induction of voltages within internal circuits or external leads of the device) of the device due to the gradient magnetic field of an MR scanner. Testing per ISO/TS 10794 clause 16	The functionality of the device being tested shall not be affected.	No device malfunction has been reported.
Radio Frequency Induced Malfunction	To evaluate the radio frequency (RF) induced malfunction. Testing per ISO/TS 10794 clause 15	The functionality of the device being tested shall not be affected	No device malfunction has been reported.
Imaging Artifact	To measure the image artifact induced by the device when exposed to MR scan using different types of sequences. Testing per ASTM F2119-07	Compliance is verified if product labeling (IFU) contains information about the size of the imaging artifact.	This input is implemented into the IFU.
Biocompatibility Testing			
Test	**Purpose**	**Acceptance Criteria**	**Results**
Genotoxicity (AMES – Bacterial Reverse Mutation)	Evaluation of mutagenic potential of the device. Testing per ISO 10993-3	Number of mean revertants of test article <2 of the means obtained from the control blank, for strains TA98, TA100 or WP2uvrA; or <3 of the means obtained	**PASS**

		from the control blank for strains TA1535 or TA1537; with or without metabolic activation system.	
Genotoxicity (Chromosomal Aberration)	Evaluation of clastogenic potential of the device. Testing per ISO 10993-3	No statistically significant difference between TA98, TA100 or WP2uvrA;	**PASS**
Cytotoxicity	Evaluation of cytotoxic potential (cellular toxicity) of the device. Testing per ISO 10993-5	Cell viability of test article extract ≥ 70%	**PASS**
Intracutaneous Irritation	Evaluation of irritant potential (intracutaneous irritation) of the device. Testing per ISO 10993-10	Cell viability of test article edema ≤ 1.0	**PASS**
Sensitization Test	Evaluation of allergic potential (delayed dermal sensitization) of the device. Testing per ISO 10993-10	Result of test article extract overall mean score lower than the most severe corresponding control blank score for erythema and edema.	**PASS**
Acute Systemic Toxicity	Determination of systemic hazards of the device. Testing per ISO 10993-11	No weight loss >10%, no clinical signs of marked toxicity (according to the following table) or mortality on more than 2 mice	**PASS**
Pyrogenicity (Rabbit Pyrogen Test)	Determination of pyrogen substance presence in the device. Testing per USP 41–NF 36 <151> and Ph. Eur. Section 2.6.8	Temperature increase ≤0.5°C (for each rabbit compared to the initial temperature)	**PASS**

Local Tolerance	To provide in vivo evaluation of the local tissue reaction of the cochlear implant compared to negative control material (HDPE) after subcutaneous implantation in rabbit for a short-term or long-term.Testing per ISO 10993-6	Qualitative and semi-quantitative histopathologic evaluation of the local tissue effects.	**PASS**

The table below summarizes the laboratory studies performed on the **Neuro 2 Sound Processor**.

Test	**Purpose**	**Acceptance Criteria**	**Results**
Mechanical Testing			
Test for Free Fall Shock for Neuro 2 Sound Processor	To evaluate the robustness of Neuro 2 SP to withstand the mechanical forces that might occur during transit, storage and normal conditions of use. Testing per ANSI AAMI CI86 Section 26.2.4.	Acoustic performance: No degradation of performance Visual performance: Scratches, impression marks are acceptable. Electrical performance: No degradation of performance, Mechanical performance: No degradation of performance. Opening of battery drawer and loss of battery is acceptable	**PASS**

Testing for Immunity of the Neuro 2 Sound Processor Antenna Cable	To evaluate the robustness of the Neuro 2 SP antenna cable, which connects the Neuro 2 SP and the headpiece antenna. Testing per ANSI AAMI CI86 Sections 26.3.1 & 26.3.6	Mechanical inspection: No mechanical changes according to product specification Visual inspection: No sharp points or edges Electrical inspection: According to the product specification	After evaluating the mechanical and electrical robustness of the Neuro 2 SP antenna cable, there was: – No mechanical degradation of the cables – No degradation of electrical performance – No visual degradation.
Biocompatibility Testing			
Test	**Purpose**	**Acceptance Criteria**	**Results**
Cytotoxicity	Evaluation of cytotoxic potential (cellular toxicity) of the worst-case device. Testing per ISO 10993-5	Cell viability of test article extract ≥ 70%	**PASS**
Intracutaneous Irritation	Evaluation of irritant potential (intracutaneous irritation) of the worst-case device. Testing per ISO 10993-10	Difference between the test article extract overall mean score and the corresponding control blank overall mean score for erythema and edema ≤ 1.0	**PASS**
Sensitization Test	Evaluation of allergic potential (delayed dermal sensitization) of the worst-case device. Testing per ISO 10993-10	Result of test article extract overall mean score lower than the most severe corresponding control blank score for erythema and edema	**PASS**

The table below summarizes laboratory studies on the **CI-Link Interface**.

Test	Purpose	Acceptance Criteria	Results
Mechanical Testing			
Test for Free Fall Shock for CI-Link	The purpose of the test was to ensure that the CI-Link can withstand the mechanical forces the device might be exposed to during normal conditions of use. Testing per ANSI AAMI CI86 Section 26.2.4.2	**Mechanical integrity**: No visual damage shall be observed after tests on the DUT surfaces (top, bottom, front, rear, right, left) **Functional integrity**: Connect to test computer and devices for checking proper operation of the DUT after tests (dedicated test program)	After exposure to mechanical shock: – Mechanical performance is not degraded with inspection of mechanical integrity. Electric performance continues to function according to specification. Visual performance is acceptable, with tolerable scratches and impression marks.
Test for Free Fall Shock for Programming Adaptor	The purpose of the test was to ensure that the Programming Adaptor can withstand the mechanical forces the device might be exposed to during normal conditions of use. Testing per ANSI AAMI CI86 Section 26.5.4.2	**Mechanical performance**: No degradation of performance. **Electrical performance**: No degradation of performance. **Visual performance**: No degradation of performance.	After exposure to mechanical shock: – Mechanical performance is not degraded with inspection of mechanical integrity and no evidence of mechanical hazards. – Electric performance continues to function according to specification. Visual performance is acceptable, with tolerable scratches and impression marks.
Biocompatibility Testing			
Cytotoxicity	Evaluation of cytotoxic potential (cellular toxicity) of the device Testing per ISO 10993-5	Cell viability of test article extract ≥ 70%	**PASS**

Intracutaneous Irritation	Evaluation of irritant potential (intracutaneous irritation) of the device Testing per ISO 10993-10	Difference between test article extract overall mean score and corresponding control blank overall mean score for erythema and edema ≤ 1.0	**PASS**
Sensitization Test	Evaluation of allergic potential (delayed dermal sensitization) of the device Testing per ISO 10993-10	Result of test article extract overall mean score lower than the most severe corresponding control blank score for erythema and edema	**PASS**

The table below summarizes the laboratory studies performed on the **Neuro Cochlear Implant System**.

Test	Purpose	Acceptance Criteria	Results
Electrical Safety Testing			
Insulation Diagram	To verify that the NCIS is insulated safely during patient use. Testing per ANSI AAMI ES60601-1	**For 1 MOOP; 5V-DC: Area A & D** - Creepage requirement verified - Clearance requirement verified **For 1 MOPP; 240V-AC: Area B & C** - Creepage requirement verified - Clearance requirement verified	**PASS**

	To determine the leakage current following different use cases and the working voltage. Testing per ANSI AAMI ES60601-1	**For leakage current measurements**: – Touch Current (TC): < 100µA NC; – <500µA for SFC – Patient Leakage Current (DC current): <10µA NC; <50µA SFC – Patient Leakage Current (AC current): <100µA NC; <500µA SFC – Patient Leakage Current with External Voltage on Signal Input/Output (DC current): <10µA NC; <50µA SFC – Patient Leakage Current with External Voltage on Signal Input/Output (AC current): <100µA NC; <500µA SFC – Patient Leakage Current with External Voltage on Metal Accessible Part: <500µA – Patient Auxiliary Current (DC current): <10µA NC; <50µA SFC – Patient Auxiliary Current (AC current): <100µA NC; <500µA SFC – Total Patient Leakage Current (DC current): <50µA NC; <100µA SFC – Total Patient Leakage Current (AC current): <500µA NC; <1000µA SFC For working voltage measurements: – Does not exceed 42.4 V peak (AC current) or 60V (DC current) in NC or SFC. **NC**: Normal Condition **SFC**: Single Fault Condition.	**PASS**

Dielectric Strength Test of Solid Insulating Materials with Safety	Apply the voltage level corresponding to insulation type (1 or 2 MOOP/MOPP) following the areas defined in the insulation diagram and working voltage. Testing per ANSI AAMI ES60601-1	Check if there was any dielectric breakdown after 1 minute.	No dielectric breakdown was observed on the NCIS. The NCIS is compliant with 2 MOOP/MOPP levels.
Excessive Temperature	To evaluate the maximum temperature in normal and single fault conditions for different components of the NCIS. Testing per ANSI AAMI ES60601-1	Maximum allowable temperatures shall not be exceeded.	Maximum allowable temperatures were not exceeded when the NCIS operated in both normal and single fault conditions.
Power or Energy Dissipation	To verify that power and energy dissipation pose no safety risks to the patient during single fault condition use of the NCIS Testing per ANSI AAMI ES60601-1	Maximum power dissipated < 15W Maximum energy dissipated < 900 J	The maximum power dissipation of the NCIS was 2.5W. Note that the NCIS has a dissipated power less than 5W because the system is supplied by a computer (5V/500mA) with protected output compliant with IEC 60950-1.
FCC Radio Tests			
Radiated Spurious Emission 9kHz to 30MHz	To evaluate whether the NCIS radiates spurious emissions for the frequency range 9 kHz to 30MHz. Testing per 47 CFR part 15.	Be under the limit for a given frequency range.	**PASS**

Radiated Spurious Emission 30MHz to 1GHz	To evaluate whether the NCIS radiates spurious emissions for the frequency range 30 MHz to 1GHz. Testing per 47 CFR part 15.	Be under the limit for a given frequency range.	**PASS**
Electromagnetic Compatibility Testing			
Radiated Emissions	To evaluate the NCIS on emitted radiated disturbance for frequency range 30 MHz- 1 GHz. Testing per CISPR 11	**For Class A (Professional use)**: For frequency 30 MHz to 230 MHz: Quasi peak < 50µV/m For frequency 230 MHz to 1GHz: Quasi peak < 57µV/m **For Class B (Patient use)**: For frequency 30 MHz to 230 MHz: Quasi peak < 40µV/m For frequency 230 MHz to 1GHz: Quasi peak < 47µV/m	The NCIS is compliant for Class A and B for radiated emissions. All measurements were within the limits.
Immunity – Electrostatic Discharge	To evaluate the immunity of the NCIS against electrostatic discharge. Testing per IEC 61000-4-2	**Electrical function**: The implant is considered functional when communication is maintained between the Neuro 2 Sound Processor, CI-Link Fitting Interface, and the PC.	The NCIS is compliant with all electrostatic discharge tests.
Immunity – RF Electromagnet- ic Fields	To evaluate the immunity of the NCIS against radiated, radio-frequency electromagnetic fields. Testing per IEC 61000-4-3	**Electrical function**: The implant is considered functional when communication is maintained between the Neuro 2 Sound Processor, CI-Link Fitting Interface, and the PC.	The NCIS is compliant with all RF electromagnetic field tests.

Immunity - Proximity Fields from RF Wireless Communica-tions Equipment	To evaluate the immunity of the NCIS against proximity fields from RF wireless communications equipment. Testing per IEC 61000-4-3	**Electrical function**: The implant is considered functional when communication is maintained between the Neuro 2 Sound Processor, CI-Link Fitting Interface, and the PC.	The NCIS is compliant with all RF wireless communication tests.
Immunity - Power Frequency Magnetic Fields	To evaluate the immunity of the NCIS against power frequency magnetic fields. Testing per IEC 61000-4-8	**Electrical function**: The implant is considered functional when communication is maintained between the Neuro 2 Sound Processor, CI-Link Fitting Interface, and the PC.	The NCIS is compliant with the power frequency magnetic field test.
Immunity - Conducted Disturbances, Induced by Radio Frequency Fields	To evaluate the immunity of NCIS against conducted disturbances induced by radio frequency fields. Testing per 61000-4-6	**Electrical function**: The implant is considered functional when communication is maintained between the Neuro 2 Sound Processor, CI-Link Fitting Interface, and the PC.	The NCIS is immuneto the conducted disturbances, induced by radio frequency fields according to IEC 61000-4-6: 2013.
Immunity – Electromagnet- ic Emissions from Radio-Frequency-Identification (RFID) Readers.	To evaluate the immunity of NCIS against emission from radio-frequency-identification (RFID) readers. Testing per AIM 7351731	No overstimulation that could lead to patient permanent damage according to ANSI/AAMI CI86:2017 §17.3.	The NCIS is immune to the electromagnetic emissions from radio-frequency-identification (RFID) readers according to AIM 7351731.
Immunity – Radiated magnetic fields from 16.6 Hz to 27 MHz	To evaluate the immunity of NCIS against radiated disturbances from magnetic fields from 16.6 Hz to 27MHz. Testing per ISO 14708-3	**Criteria A** : When applying LOW level magnetic fields: No stimulations above the "Comfort level." EUT may stop functioning, but recovers after exposure without user intervention. **Criteria B**: When applying HIGH level magnetic fields: No overstimulation that could lead to patient permanent damage according to ANSI/AAMI CI86:2017 §17.3.	The NCIS is immuneto radiated magnetic fields from 16.6 Hz to 27 MHz according to ISO 14708-3:2017.

Immunity - Radiated Pulsed Electrical fields from 10MHz to 2.7 GHz	To evaluate the immunity of NCIS against radiated disturbances from high electrical fields from 10MHz to 2.7GHz. Testing per ISO 14708-7	**Criteria A**: When applying LOW level magnetic fields: No stimulations above the "Comfort level." EUT may stop functioning, but recovers after exposure without user intervention. **Criteria B**: When applying HIGH level Magnetic fields: No over stimulation that could lead to patient permanent damage according to ANSI/AAMI CI86:2017 §17.3.	The NCIS is immune to radiated pulsed electric fields from 10 MHz to 2.7 GHz according to ISO14708-7:2019.
Immunity - Radiated Electrical Fields from 80MHz to 2.7 GHz	To evaluate the immunity of NCIS against radiated disturbances from electrical fields from 80MHz to 2.7GHz Testing per ISO 14708-3	No over stimulation that could lead to patient permanent damage according to ANSI/AAMI CI86:2017 §17.3.	The NCIS is immuneto radiated electric fields from 80 MHz to 2.7 GHz according to ISO14708-3:2017.
Immunity - Proximity Field from RF Wireless Communications	To evaluate the immunity of NCIS against radiated disturbances caused by RF wireless communications equipment from 385MHz to 5.8GHz Testing per IEC 61000-4-3.	No overstimulation that could lead to patient permanent damage according to ANSI/AAMI CI86:2017 §17.3.	The NCIS is immuneto radiated proximity fields from RF communications according to IEC 61000-4-3.

The table below summarizes the laboratory studies performed on the **Non Sterile Surgical Tools**.

Test	Purpose	Acceptance Criteria	Results
Cytotoxicity	Evaluation of cytotoxic potential (cellular toxicity) of all surgical tools after in-house final cleaning, after 1 cycle of each reprocessing procedure (manual and automatic) and after 240 cycles (representative of the tool's lifetime) of each reprocessing procedure. Testing per ISO 10993-5	Cell viability of test article extract ≥ 70%	**PASS**
Intracutaneous Irritation	Evaluation of irritant potential (intracutaneous irritation) of the worst-case devices after in-house final cleaning and after 1 cycle of each reprocessing procedure (manual and automatic). Testing per ISO 10993-10	Difference between the test article extract overall mean score and the corresponding control blank overall mean score for erythema and edema ≤1.0	**PASS**
Sensitization Test	Evaluation of allergic potential (delayed dermal sensitization) of the worst-case devices after in-house final cleaning Testing per ISO 10993-10	Result of the test article extract overall mean score is lower than the most severe corresponding control blank score for erythema and edema.	**PASS**
Acute Systemic Toxicity	Determination of Systemic toxicological risk of the worst case devices after in-house final cleaning Testing per ISO 10993-11	No weight loss >10%, no clinical signs of marked toxicity (according the following table) or mortality on more than 2 mice	**PASS**
Pyrogenicity (Rabbit Pyrogen Test)	Determination of pyrogen substance presence in the worst-case devices after in-house final cleaning. Testing per USP 40-NF 35 Chapter <151>	Temperature Increase ≤0.5°C (for each rabbit compared to the initial temperature)	**PASS**

B. Additional Studies

Chemical and Biochemical Characterization			
Extensive Chemical Characterization Program on Post-Production Implants and on Aged Implants (3-year Accelerated Aging)	No new types of extractables or leachables detected. Equivalent or lower levels for common extractable and leachable substances. Testing per standards ISO 10993-18 and ASTM F 1980	Post-production implants (cleaned, packaged and sterilized) and accelerated aged implants (final packed and sterilized implants placed in a temperature-controlled incubator for 85 days; representative of three-year real time shelf life) were exhaustively extracted in two identified solvents (PW, EtOH). The prepared extracts were then analyzed using FTIR, ICP- MS, HPLC-IC, GC-MS, UPLC-MS and HS GC-MS.	**PASS**
Reprocessing Cleaning Procedures Efficiency of Non Sterile Surgical Tools	No visible residues should be detected on the device at the end of each cycle. Residual protein < 6.4µg/cm2 for each test device and residual hemoglobin < 2.2µg/cm2 for each test device. Testing per standards EN ISO 17664, ANSI AAMI ST81	Worst-case devices were soiled then subjected to successive reprocessing cycles using both procedures recommended in the IFU (manual and automatic) to simulate multiple reuses and represent clinical conditions. The reprocessed devices were then soiled and cleaned according to worst-case parameters for each cleaning method and analyzed for residual protein and hemoglobin	**PASS**

Stimulation Safety Validation

All parameters related to the NCIS stimulation safety were calculated and measured. Direct current leakage was ensured kept below the safe limit of 0.1 µA following the stimulation conditions described in the ANSI/AAMI CI86 Section 17.2. The charge and charge density were calculated and measured in accordance with the tests described in the ANSI/AAMI CI86 Section 17.3, to be below the safe limits of 468 nC and 216 $nC.cm^{-2}$. The balance of charges

between anodic and cathodic phases were measured in conformity with the ANSI/AAMI CI86 Section 17.5.

In addition, supplementary material and information were provided to support the description of the NCIS stimulation and stimulation safety. The description of this unique stimulation was provided with a computational model to help show the relation existing between the anodic and its following cathodic capacitive phase. Finally, the long term effect of the NCIS stimulation on the physical electrode contact was evaluated with (1) a theoretical calculation from a literature review and prediction of electrode corrosion considering worst case stimulation parameters, and (2) an analysis of the electrode profiles from explanted legacy cochlear implant systems. Since 2004, the company has analyzed more than 900 explants. None of them showed any significant sign of electrode corrosion which would indicate issues related to excessive charge density. In particular, two devices received after 5 to more than 17 years of use were analyzed in detail and did not show any trace of electrode corrosion. Both the theoretical calculation and the explant analysis showed electrode geometries in conformity with their specifications with no critical modification of shape, surface area, and mass.

Sterilization Validation

The Neuro Zti Implant (CLA and EVO) and the sterile surgical tools, parts of the NCIS, are sterilized respectively by ETO or by steam. The sterilization method was validated to a sterility assurance level (SAL) of 10^{-6} per ISO 11135:2014 (Sterilization Of Health-Care Products - Ethylene Oxide - Requirements For The Development, Validation And Routine Control Of A Sterilization Process For Medical Devices [Including: Amendment 1 (2018)]) and ISO 17665-1:2006 (Sterilization Of Health Care Products -- Moist Heat -- Part 1: Requirements For The Development, Validation, And Routine Control Of A Sterilization Process For Medical Devices).The reusable surgical tools within the NCIS are sold unsterilized. However, the sterilization method was validated to a sterility assurance level (SAL) of 10^{-6} per ISO 17665-1:2006 (Sterilization Of Health Care

Products -- Moist Heat -- Part 1: Requirements For The Development, Validation, And Routine Control Of A Sterilization Process For Medical Devices).

Bacterial Endotoxin Testing

Routine limulus amebocyte lysate (LAL) batch release testing is performed for every sterile load of the NCIS using the USP chapter <85> Bacterial Endotoxins Test. The implants and the sterile surgical tools are held to the specification of ≤ 2.15 EU/device in accordance with ANSI/AAMI ST72.

Shelf Life and Packaging Validation

The implant (EVO and CLA) and the sterile surgical tools were separately tested and determined to have a 3-year shelf life. The 3-year shelf life was verified on accelerated time aged devices. The samples were conditioned for shipping and sterilized. The implant (EVO and CLA) functionality and hermeticity were tested and met acceptance criteria. In addition, packaging integrity was verified and met acceptance criteria to support the 3-year shelf life.

This testing was conducted per ASTM F 1929.

Transportation Testing

The different parts of the NCIS were separately tested for transportation. Their functionality, as well as the label marking and the robustness of the sale packaging was tested and met the acceptance criteria.

This testing was conducted per ASTM D 4169.

Lithium-Ion Battery Testing

Both large and small batteries were tested to demonstrate and justify that transport is safe. These tests were performed according UN transportation manual of tests and criteria, and according to IATA UN 3480 (2014). The batteries underwent altitude simulation, thermal test, vibration, shock, external short circuit, crush, overcharge and forced discharge tests.

Successful tests were performed according to UL 1642:2013, UL 2054:2004, IEC 62133:2012 and IEC 60601-1-2:2014-02 and IEC/EN 61000-4-2:2008/2009.

Finally, performance testing such as Rechargeable battery fade test were performed successfully and were compliant with ANSI/AAMI CI 86:2017.

Charger Testing

Tests were performed to justify the electrical safety of the charger. It has been proved that the product fulfills all the requirements of the standard EN 60950-1:2006+A11:2009+A1:2010+A12:2011+AC:2011+A2:2013.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of cochlear implantation with the NCIS in subjects 18 years and older with severe-to-profound sensorineural hearing loss outside of the US. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Subjects were treated between February 2, 2017 and December 11, 2018. The database for this PMA reflected data collected through December 9, 2019 and included 53 subjects, among whom 51 subjects underwent cochlear implant surgery (see below for further details on the PMA Cohort Accountability). There were 6 OUS investigational sites (5 in Canada and 1 in Denmark).

This study is titled "The Neuro Zti Cochlear Implant System Effectiveness and Safety in Adults – Pivotal Study." The study was designed as a prospective, multi-center, one-arm, non-randomized, non-blinded, repeated-measures clinical study. The safety and effectiveness data were collected throughout the duration of the 12 months study. Each subject served as her or his own control; post-implant performance was compared to each subject's baseline (pre-implant) performance.

This study included a Data Safety Monitoring Board (DSMB) to monitor participant safety during the study.

Investigational Sites

The following list identifies the 6 OUS investigational sites (a-e in Canada; f in Denmark); the number of subjects enrolled at each site is identified in parentheses:

a. Ottawa Hospital – Civic Campus (2)
b. CHU de Québec / L'Hôtel-Dieu de Québec (8)
c. Sunnybrook Health Science Centre (15)
d. Royal University Hospital (7)
e. Nova Scotia Hearing and Speech Centres (11)
f. Øre-næse-halskirurgik & Audiologisk Klinik Undefunktionen på Gentofte Hospital (8)

1. Clinical Inclusion and Exclusion Criteria

Enrollment in this study was limited to patients who met the following inclusion criteria:

- Signed written informed consent form prior to any study related activities,
- Aged ≥ eighteen (18) years,
- Bilateral severe-to-profound sensorineural hearing loss, pure tone audiometry (PTA) ≥ 70 dB HL (average of the thresholds for pure tones at 500, 1000 and 2000 Hz, in both ears),
- Post-lingual onset of deafness,
- Limited benefit from appropriately fitted hearing aid(s), defined as ≤ 50% correct in HINT sentences recognition in quiet, binaurally in the best listening condition,
- Primary implantation, i.e., not previously implanted (not a previous cochlear implant user who was explanted),
- No anatomical contraindications: Radiological evaluation showing no obstacles to full electrode insertion and verifying the absence of central auditory lesions,
- Fluent in local language (e.g., 34 English-speaking subjects, 8 Danish-speaking subjects, and 8 French-speaking subjects), including reading and writing,
- Psychologically suitable,
- Updated pneumococcal vaccine

Patients were not permitted to enroll in this study if they met any of the following exclusion criteria:

- Medical conditions that contraindicate undergoing surgery (middle ear diseases such as AOM (Acute Otitis Media)/CSOM (Chronic Suppurative Otitis Media), lesions of auditory nerve, pathologies of central auditory pathway, otosclerosis, any cochlear malformation such as Mondini malformation, cochlear ossification, large vestibular aqueduct),
- Unrealistic expectations from the candidate regarding the possible benefits, risks, and limitations that are inherent to the surgical procedure(s) and the device,
- Unwillingness or inability of the candidate to comply with all investigational requirements.

2. Follow-up Schedule

All subjects were scheduled to return for follow-up examinations at 14 days post-surgery (-7 days, +6 days), 1 month post-surgery (-3 days, +6 days) (corresponding to device activation date), 3 months- , 6 months- and 12 months- post-activation (-7 days, +6 days).

To fulfill pre-operative considerations, all participants had a tympanometry and CT-scan or MRI imaging, pure tone audiometry in both ears and a speech perception test with HINT sentence test. The HINT sentence tests were conducted on both ears with the best fitted hearing aid(s) in quiet and in noise. The HINT sentences were presented at a conversational speech level of 60 dB SPL in quiet, and in steady speech-shaped noise, with the sentences presented at +10 dB SNR, with noise set at 55 dB SPL, and signal at 65 dB SPL. The noise and/or the signal were presented in front of the participant at 0° azimuth.

Pre-operatively, ECAP and impedance measures were performed after the cochlear implantation surgical procedure. Post-operatively, the parameters measured included ECAP and electrodes impedance at device activation and subsequent visits. The HINT sentence tests were performed in quiet and in noise, at same pre-operative presentation levels, after 3, 6 and 12 months of device use (see **Table 1**). The speech understanding assessment with the HINT sentence test was performed on ipsilateral ear with activated NCIS and occluded contralateral ear with ear plug. Adverse events and complications were recorded at all visits.

The key timepoints are shown below in the tables summarizing safety and effectiveness.

Table 1: Study Assessment Schedule

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				
Subject 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. Clinical Endpoints

Safety Endpoint: The primary safety endpoint was the number and proportion of individuals experiencing an adverse event, defined as any major or minor complications, which are further described below. Safety data was collected through the duration of the study, captured as the type and duration of any adverse event(s), and classified as major or minor complications. Evaluations were performed from baseline, during the operative time, and at each time point.

The applicant did not propose formal statistical hypothesis testing for the safety endpoint. Descriptive statistics of adverse events were provided on a minimum of 50 surgeries, and observed rates of major adverse events were compared to rates reported in the scientific literature for similar devices.

Safety assessment: All complications/adverse events were 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 reimplantation (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 (and non-implantable parts including the sound processor and accessories) returned to the manufacturer were to be analyzed.

Effectiveness Endpoints:

Primary Effectiveness Endpoint: The primary effectiveness endpoint with the NCIS was defined for the English-speaking participants as the difference between HINT-Q scores obtained at 6 months post-activation with their cochlear implant alone and pre-operative, best-aided scores.

A clinical benefit of 50 percent points was expected, and the success criterion for the primary effectiveness endpoint was defined as a clinical benefit of greater than 20 percent points (in terms of improvement at 6 months).

Statistical analysis of the primary effectiveness endpoint was performed using a one-sided alpha level of 0.025. In a one-sample t-test, the difference between HINT-Q scores at 6 months post-activation with the cochlear implant alone and pre-operative, best-aided baseline (m) was compared against a theoretical mean (μ) of 20 (%).

The pre-specified null and alternative hypotheses are as follows:

$$H0: m \leq \mu$$

or H0: the average clinical benefit (m) at 6 months is smaller or equal to 20%,

and

$$Ha: m > \mu \text{ (greater)}$$

or Ha: the average clinical benefit (m) at 6 months is greater than 20%.

The consistency of the primary endpoints was examined across investigational sites by testing for an effect of site in an ANOVA model.

Secondary Effectiveness Endpoints: The secondary effectiveness endpoints with the NCIS were defined for the English-speaking participants as: 1) the difference between HINT-Q obtained at 3 and 12 months post-activation with their cochlear implant alone and pre-operative, best-aided scores; and 2) the difference between HINT-N scores obtained at 3, 6, and 12 months post-activation with their cochlear implant alone and pre-operative, best-aided scores. All secondary or sensitivity analyses are supportive analyses to the primary effectiveness endpoint. No hypotheses were pre-specified for these secondary endpoints.

Speech recognition assessment: The HINT (Hearing in noise Test) was developed at the House Ear Institute (Los Angeles, California) and measures speech recognition thresholds in quiet and in noise. When used to determine cochlear 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. In the present study, subjects were tested with two sentence lists, presented from a software-controlled digital recording: at inclusion (visit 2) in quiet and in noise, both in the best aided condition, and at 3, 6- and 12-months post-activation (visits 6, 7 and 8 respectively) in quiet and in noise, in the ipsilateral electrically stimulated ear with an occluded contralateral ear. In quiet, sentences were presented at a conversational speech level of 60 dB SPL. In noise, sentences were presented at fixed +10dB SNR, with noise set at 55 dB SPL, and signal at 65 dB SPL. The noise and/or the signal was presented from the front of the recipient at 0° azimuth.

B. Accountability of PMA Cohort

Fifty-three (53) subjects were included in the OUS study, among which two (2) subjects could not undergo NCIS surgery. Of these two subjects, one died from unrelated causes between inclusion and the surgery, and the other subject did not receive NCIS due to a surgical failure (due to a previously undiscovered cholesteatoma and described further below), leaving 51 subjects in the Safety Analysis Set (SAS) population. At the time of database lock, of 51 subjects in the SAS population, 98.04% (50) subjects are available for analysis at the completion of the study, the 12 month post-operative visit, and 45 subjects completed the study per protocol (Per Protocol population).

A flowchart of the analysis populations is provided in Figure 5, as well as the population definitions.

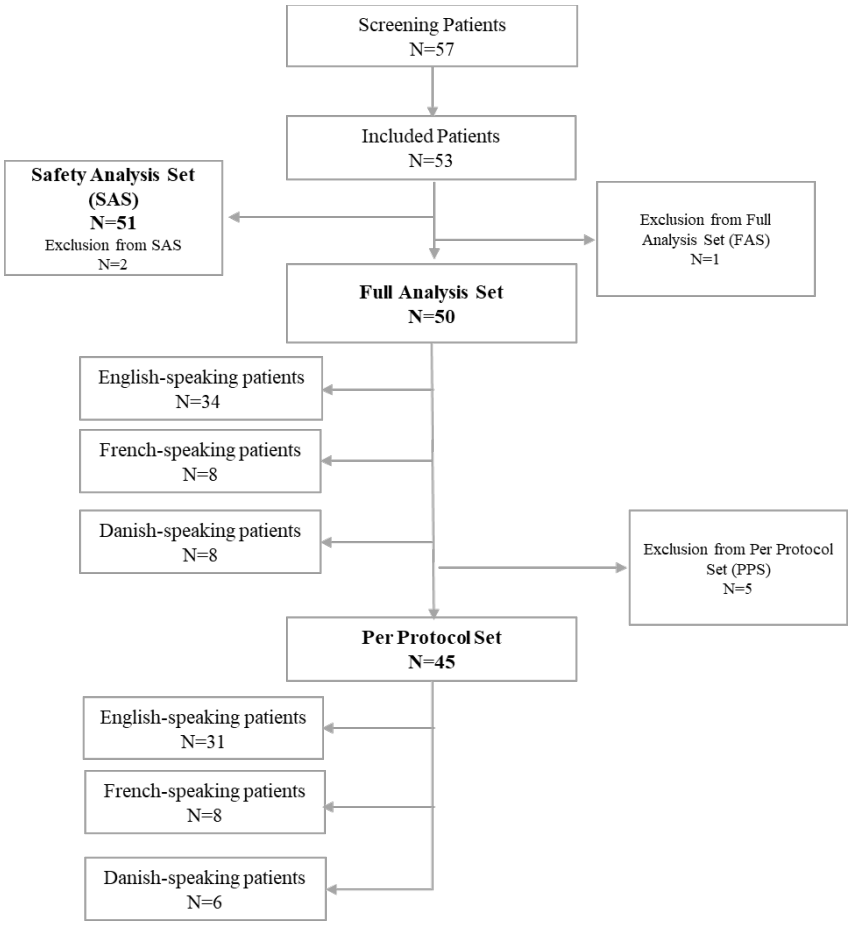

Figure 5: Population Disposition Diagram

Safety Analysis Set (SAS): All subjects for whom the surgery of implantation started (n=51).

Full Analysis Set (FAS): All subjects implanted with the device, regardless of whether any post-operative data are available (n=50).

Per Protocol Set (PPS): All subjects of the FAS who completed the study according to the protocol (n=45).

Safety results are presented in SAS population, and effectiveness results are reported in FAS and PPS for the native English-speaking subjects.

Table 2 presents subject accountability in the clinical study. Among the 51 subjects in the SAS population, 50 were successfully implanted; one subject could not be implanted because of a middle-ear pathology, a cholesteatoma, discovered during the surgery that was not detected during the pre-operative cochlear implant assessment. The surgical procedure for cochlear implantation was converted into a cholesteatoma removal surgery.

Among the 50 subjects who were successfully implanted, 34 native English-speaking participants were followed up to assess their speech recognition performance. Among the 34 subjects, 33 completed all speech recognition measures. Speech recognition performance from one subject was not evaluated at the 3-month visit only due to non-compliance with the follow-up test sessions.

Table 2: Subject Accountability

	V1 Screening	V2 Inclusion	V3 Surgery	V4 Follow-up	V5 Activation	V6 Visit M3	V7 Visit M6	V8 Visit M12
Theoretical	57	57	57	57	57	57	57	57
Deaths (cumulative)	0	0	1	1	1	1	1	1
Failures (cumulative)	0	4	5	6	6	6	6	6
Expected	57	53	51	50	50	50	50	50
Actual [A]	57	53	51	50	50	49	50	50
Actual [B]	57	53	51	50	50	49	50	50
% Follow-up	100.00	92.98	89.47	87.72	87.72	85.96	87.72	87.72

A: Patients with complete data for each endpoint, evaluated per protocol, in the window time frame.

B: Patients with any follow-up data reviewed or evaluated by investigator ("all evaluated" accounting).

Device Configuration

All subjects were implanted unilaterally with a Neuro Zti Implant with an EVO electrode array. Subjects had their initial activation (mapping) approximately one month after surgery with a Neuro One Sound Processor. The Oticon Medical Neuro Cochlear Implant System is distributed in the

United States with the next-generation Neuro 2 Sound Processor. Neuro One and Neuro 2 sound processors have been demonstrated to be equivalent in terms of end-to-end acoustic-electric performance as the Neuro 2 Sound Processor is essentially a re-packaging of the Neuro One sound processor electronic components (see rest of this section for supporting details). Compared to Neuro One, Neuro 2 constitutes a design upgrade, with a smaller and lighter behind-the-ear (BTE) design, expanded battery options, and improved dust and humidity resistance (meeting IP68 rating). Neuro 2 also has additional compatible accessories (e.g., compatibility with an off-the-shelf wireless streamer device) than Neuro One. Both sound processors operate with the same signal processing algorithms (coordinated adaptive processing – CAP) and sound treatment features.

The equivalence of the signal processing algorithms in Neuro One and Neuro 2 was assessed using bench simulations reproducing the signal processing pipelines of both sound processors, with the outputs converted into electrodograms. Electrodograms represent the electrical stimulation pattern occurring in the 20 electrodes of the Neuro Zti implant part of the NCIS when one acoustic input is presented to the sound processor (see upper and middle row in **Figure 6**). Electrodograms allow a verification of the equivalence of the entire cochlear implant system, from sound capture to electrical stimulation. Two controlled sound inputs were used for comparison, the VCV (vowel-consonant-vowel) logatome /A-SH-A/ (0.7 sec. long) and a longer sentence (3 sec. long). The method used for comparing electrodograms first derives a cost function (lower left panel in **Figure 6**) comparing the two electrodograms while taking into account the relative contribution of low- and high-energy pulses and finally a binary difference map (lower right panel in **Figure 6**) summarizing the meaningful differences detected between the two electrodograms. The difference in output as measured by this method between Neuro One and Neuro 2 sound processors when using the logatome or the sentence as acoustic inputs was respectively 0.8% and 0.5% of the total energy contained in the binary maps. This difference represents a negligible fraction of the input signal and is not expected to have any impact on sound perception or clinical performance. In order to further demonstrate this last point, the short-time objective intelligibility (STOI), a metric of speech-signal intelligibility, was computed for both Neuro One and Neuro 2 outputs and no significant difference between STOI measures was found across sound

processors. Neuro One and Neuro 2 sound processors can be considered as equivalent from a clinical perspective.

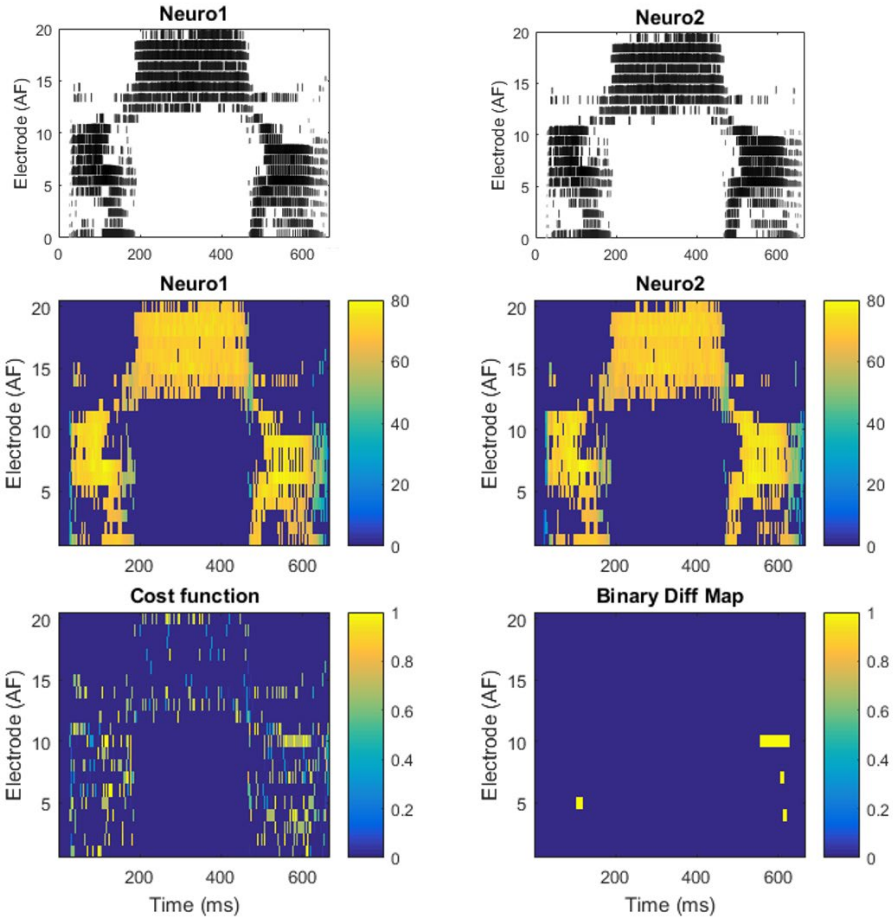

Figure 6: Direct output (electrodograms) comparison between Neuro One and Neuro 2 Sound Processor for the same input logatome /A-SH-A. Amplitude-coded electrodograms of Neuro One (left) and Neuro 2 (right) in grey-scale (top-row) or color-scale (middle row). Bottom-row: difference as cost function (left) or binary difference map (right).

Study subjects were all mapped with the Crystalis CAP coding strategy, with a default omnidirectional microphone set to opti-omni. Clinical benefits with the Neuro One or Neuro 2 sound processors are expected to be the same based on published literature (see XI. Summary of Supplemental Clinical Information below).

The NCIS provides 4 sound processing strategies, Crystalis CAP (default), Crystalis XDP, MPIS XDP, and MPIS CAP. These strategies are differentiated by the method by which channels are selected for stimulation (MPIS or Crystalis) and the compression function (XDP or CAP). The sound processing strategy defines how the sound is transformed into electrical stimulation and distributed to the various stimulating electrodes. Both Crystalis and MPIS are multiband spectral extraction strategies. They are also called 'n-of-m' as they select 'n' frequency channels out of 'm' available, with the highest spectral energy in each stimulation cycle. For Crystalis and MPIS, the 'n' is adjustable from 1 to 20 (default 'n'=8). Crystalis includes a high pitch frequency filtering mechanism to provide as much information as possible to the subject. Main Peak Interleaved Sampling (MPIS) stimulates a pre-selected maximum number of electrodes per acquisition frame (i.e., an anti-crosstalk function minimizes interaction between electrodes, so two adjacent electrodes are not stimulated at the same time). Both channel selection strategies can be combined with a compression strategy, either Coordinated Adaptive Processing (CAP; default) or multiband compression function (XDP) a subset of CAP. The aim of CAP and XDP is to map the input sound level into output stimulation level. The difference is that the mapping functions are either adaptive to the input sound levels changes (CAP) or static with a fixed input sound level (XDP).

The Crystalis CAP coding strategy was evaluated in the pivotal study and the three other (non-default) sound processing strategies (Crystalis XDP, MPIS CAP, and MPIS XDP) were validated through Real-World Evidence (see XI. Summary of Supplemental Clinical Information below).

C. Study Population Demographics and Baseline Parameters

The demographics of the OUS study population are generally considered comparable for a pivotal study performed in the US (e.g., gender distribution and average age; see below for details).

The key demographics are shown in the tables below. The SAS population included subjects with a mean age of 69 years and 5 months (± 11 years and 3 months), ranging from 38 years to 89 years and 6 months. Among these subjects, 80.4% (41/51) were older than 60 years of age; 60.8% (31/51) of the included subjects were female. In terms of average age and gender distribution, these numbers correspond to the characteristics of adult populations usually involved in cochlear implant clinical trials in the U.S. [2,3].

Regarding ethnicity/race, the global prevalence of hearing loss is apparently higher among Hispanic and non-Hispanic White populations than among non-Hispanic Black populations across almost all ages [4]. This difference is still under study; both socioeconomic and physiological factors could be involved [5]. These aspects, however, are not expected to have systematic effects on safety or effectiveness outcomes observed in the study.

Table 3 presents the demographics and baseline cochlear implant candidacy characteristics of the 51 SAS subjects. The 51 SAS subjects are defined as subjects in whom the surgery for Neuro Zti CIS implantation was started in the operative room. **Table 4** presents the same data for the 34 native English-speaking subjects in the FAS. All baseline demographics and characteristics were similar between analysis populations.

Table 3: Demographics and Baseline Characteristics of SAS Population

All participants (N)	51 (100%)
Gender	
Female	31 (60.8%)
Male	20 (39.2%)
Age at implantation (years†)	69.5 ± 11.4 [38.0-89.5]
Implanted Ear (side)	
Left	22 (43.1%)
Right	29 (56.9%)
Duration of hearing loss (years†)	
Implanted ear	30.7 ± 19.0 [0.7-71.7]

Contralateral ear	33.2 ± 19.6 [0.7-71.7]
Duration of hearing aid use (years†) Implanted ear Contralateral ear	 22.2 ± 15.8 [0.0-64.6] 22.6 ± 15.8 [0.0-64.6]
Average PTA, 500 Hz to 2000 Hz (dB HL†) Implanted ear Contralateral ear	 101.3 ± 13.3 [75-120] 95.8 ± 16.3 [70-120]

† Mean ± Standard Deviation (SD) [Median] [Min-Max]

Table 4: Demographics and Baseline Characteristics in FAS English-Speaking Group

Participants (n)	34
Gender Female Male	 19 (55.9%) 15 (44.1%)
Age at implantation (years†)	70.5 ± 12.5 [72.4] [38.0-89.5]
Implanted Ear (side) Left Right	 16 (47.1%) 18 (52.9%)
Duration of hearing loss (years†) Implanted ear Contralateral ear	 30.8 ± 18.7 [29.9] [0.7-71.7] 31.7 ± 19.7 [33.5] [0.7-71.7]
Duration of hearing aid use (years†) Implanted ear Contralateral ear	 21.4 ± 16.6 [17.7] [0.0-64.6] 22.9 ± 16.2 [20.2] [0.0-64.6]
Average PTA, 500 Hz to 2000 Hz (dB HL†) Implanted ear Contralateral ear	 102.6 ± 13.7 [104.2] [75.0-120.0] 95.4 ± 15.9 [91.7] [70.0-120.0]

† Mean ± Standard Deviation (SD) [Median] [Min-Max]

Baseline speech recognition performance (i.e., pre-operative HINT scores) for the 34 FAS native English-speaking participants is reported in **Table 5**. The mean pre-operative HINT scores in quiet and in noise were 13.3 ± 16.0% and 13.3 ± 17.7%, respectively.

Table 5: Speech Perception at Baseline in FAS English-Speaking Participants Group (N=34)

Test Conditions	**% correct** **Mean ± Standard Deviation (SD) [median] [min; max] English-Speaking Subjects N=34**
HINT Sentences in Quiet (60 dB SPL)	13.3 ± 16.0 [4.0] [0.0 ; 50.1]
HINT Sentences in Noise (+10 dB SNR)	13.3 ± 17.7 [3.3] [0.0 ; 52.8]

Baseline speech recognition performance for the PPS population (i.e., 31 native English speaking participants) is similar to those in FAS; the mean pre-operative HINT scores in quiet and in noise were 12.9% ± 15.7% and 13.1% ±17.9%. respectively.

D. Safety and Effectiveness Results

1. Safety Results

Primary Safety Analysis

The primary safety endpoint was defined as the number and proportion of individuals experiencing an adverse event, defined as any major or minor complication over the 12-month study duration (for details see "Safety Endpoint" and "Safety Assessment" under 3. Clinical Endpoint, above).

All Adverse Events

A total of 71 adverse events were recorded over the 12-month follow up period. Among the 51 subjects in the SAS population, 25 (49.0%) experienced at least one adverse event of any kind, and 26 (51.0%) did not experience any adverse event.

Thirty-three (of the 71) AEs were classified as unrelated to the study procedure or device (e.g., subjects experiencing flu episodes, painful teeth extraction, or liver cancer, etc.). These events were experienced by 16 individual subjects (31.4%) and are reported in **Table 6**.

Table 6: Number and Percentage of Adverse Events (Unrelated Events)

	Reported Event	**No. of occurrence**	**% of observed over 50 surgeries**	**No. of Subjects**	**% over 51 Subjects**
Ear and labyrinth disorders	Cholesteatoma	1	2.0%	1	2.0%
	Tinnitus	2	4.0%	2	3.9%
Eye disorders	Keratitis	1	2.0%	1	2.0%
Gastrointestinal disorders	Diarrhea	1	2.0%	1	2.0%
Infections and infestations	Cystitis	1	2.0%	1	2.0%
	Bronchitis chronic NOS	1	2.0%	1	2.0%
	Influenza	1	2.0%	1	2.0%
Injury, poisoning and procedural complications	Post-procedural diarrhea	1	2.0%	1	2.0%
	Post-procedural pain	2	4.0%	2	3.9%
	Post-operative dizziness	2	4.0%	2	3.9%
	Swelling	1	2.0%	1	2.0%

	Tooth injury	1	2.0%	1	2.0%
	Traumatic hematoma	1	2.0%	1	2.0%
	Vaccination complication	2	4.0%	1	2.0%
Metabolism and nutrition disorders	Diabetes mellitus	1	2.0%	1	2.0%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Hepatic cancer	1	2.0%	1	2.0%
Nervous system disorders	Headache	1	2.0%	1	2.0%
Psychiatric disorders	Depression	1	2.0%	1	2.0%
	Insomnia	1	2.0%	1	2.0%
Renal and urinary disorders	Renal failure	1	2.0%	1	2.0%
Respiratory, thoracic and mediastinal disorders	Influenza	1	2.0%	1	2.0%
	Rhinitis seasonal	1	2.0%	1	2.0%
	Rhinorrhea	1	2.0%	1	2.0%
	Sinusitis	2	4.0%	1	2.0%
Social circumstances	Physical assault	1	2.0%	1	2.0%
Surgical and medical procedures	Middle ear lesion excision	1	2.0%	1	2.0%
Vascular disorders	Flushing	1	2.0%	1	2.0%

Not Done *Unclassified term in SOC*	Shingles	1	2.0%	1	2.0%
TOTAL	-	33	66.0%	-	-

Thirty eight (38) adverse events, experienced by 20 individual subjects (39.2%) were reported as being either related to the device or to the study procedure. These events are reported in **Table 7**.

Table 7: Number and Percentage of Adverse Events (Events Reported as Device- Or Procedure-Related)

	Reported Event	No. of occurrence	% of observed over 50 surgeries	No. of Subjects	% over 51 Subjects	% Resolved
Ear and labyrinth disorders	External ear disorder NOS	1	2.0%	1	2.0%	100.0%
	Tympanic membrane hyperemia	1	2.0%	1	2.0%	100.0%
	Tinnitus	3*	6.0%	3	5.9%	66.7%
Gastrointestinal disorders	Nausea	1	2.0%	1	2.0%	100.0%
General disorders and administration site conditions	Pain	2	4.0%	2	3.9%	100.0%
	burning sensation	1	2.0%	1	2.0%	100.0%
Infections and infestations	Bronchitis chronic NOS	1*	2.0%	1	2.0%	0.0%
Inflammation localized	General disorders and administration site conditions	1	2.0%	1	2.0%	100.0%
Injury, poisoning and procedural complications	Nausea (Post-procedural)	1	2.0%	1	2.0%	100.0%
	Post-procedural pain	9	18.0%	6	11.8%	100.0%
	Post-operative dizziness	7	14.0%	7	13.7%	100.0%
	Seroma	1	2.0%	1	2.0%	100.0%
	Stitch abscess	1	2.0%	1	2.0%	100.0%
	Swelling	1	2.0%	1	2.0%	100.0%

Nervous system disorders	Ageusia	1	2.0%	1	2.0%	100.0%
	Balance impaired NOS	1	2.0%	1	2.0%	100.0%
	Headache	2	4.0%	2	3.9%	100.0%
Unclassified term in SOC	Hot spots on device	1	2.0%	1	2.0%	100.0%
	Lack of uptake by taste buds	1	2.0%	1	2.0%	100.0%
	Reverberations	1	2.0%	1	2.0%	100.0%
TOTAL	-	38	76.0%	-	-	-

* includes the two major adverse events that were related to the study (1) or the device (1).

Major Adverse Events

A summary of major adverse events is presented below in **Table 8.**

Table 8: Major Adverse Events Summary

AE Category	Number of Major Complications / (incidence over 51 subjects from SAS population)	Description	Number of Subjects / (proportion over 51 subjects from SAS population)
Related AE Device-related Study procedure-related	2 (3.9%) 1 (2.0%) 1 (2.0%)	 Tinnitus Bronchitis chronic NOS	2 (3.9%) 1 (2.0%) 1 (2.0%)
Unrelated AE	2 (3.9%) 1 (2.0%) 1 (2.0%)	 Hepatic cancer Renal failure	2 (3.9%) 1 (2.0%) 1 (2.0%)

A total of four major adverse events, experienced by four subjects, were recorded during the study. Among them, two major adverse events were classified as related to the device or the procedure, for an incidence rate of related major

adverse events of 3.9% (2 complications recorded in 2 of the 51 subjects). These events are among those identified with an asterisk in **Table 7** and summarized in **Table 8**.

One major complication related to the study procedure. Specifically, the subject experienced an exacerbation of a pre-existing chronic obstructive pulmonary disease (COPD), requiring re-admission to the hospital for 5 days of treatment. Subjects with COPD require specific anesthetic management and are at higher risk for anesthesia complications.

The other major complication related to the device. Specifically, the subject experienced tinnitus (sensation of ringing in the ear). This adverse event occurred in this subject who did not have a documented history of tinnitus prior to implantation. According to the subject, the experienced tinnitus was mild just after the surgery, and rose to a moderate level during the study period. Despite this adverse event, this subject continued using his cochlear implant system throughout the entire study period. Tinnitus is a known risk of cochlear implant surgery, and was included as an anticipated adverse event in the protocol of the clinical study.

Minor Adverse Events

A summary of minor adverse events is presented in **Table 9.**

Table 9: Minor Adverse Events

AE Category	Number of Minor Complications (incidence over 51 subjects from SAS population)	Number of Subjects (proportion over 51 subjects from SAS population)
Related AE	36 (70.6%)	20 (39.2%)
Device-related	16 (31.4%)	12 (23.5%)*
Study procedure-related	20 (39.2%)	10 (19.6%)*
Unrelated AE	31 (60.1%)	15 (29.4%)

** Some subjects experienced multiple minor AEs, and some subjects experienced device-related and procedure-related AEs.*

A total of 67 minor adverse events were recorded in 24 out of the 51 subjects (all minor events subject rate: 47.1%). Among these, 36 events were device- or procedure-related, and occurred in 20 unique subjects of the SAS population (39.2% of subjects experienced at least one related minor adverse event over the course of the study). Sixteen (31.4%) minor device-related complications were recorded during the clinical study. Among these complications, 13 concerned the implantable part, and the most frequently reported events included: a sensation of pain (6), usually occurring over the implant zone, or a sensation of dizziness (4). All other events were reported only once, including the following: a sensation of hot spot over the device, a subjective balance reduction, or intermittent headaches. Three (3) device related adverse events were related to routine use of the Sound Processor: a sore pinna (1), an irritated earlobe (1), and the perception of reverberant sounds after activation (1). These complications are risks known to be associated with cochlear implantation and are included in Section 9 (Potential Adverse Effects of the Device on Health).

The 20 minor procedure-related adverse events comprised post-procedural pain (in the wound area) (5), post-operative dizziness (3), post-operative nausea (2), and temporary tinnitus sensation (2). All other events were observed only once: one case of inflammation at the incision site related to a suture knot, a burning sensation at the implant site, a stitch abscess, excessive swelling over the implant, seroma over the skin flap, one hemotympanum (bleeding inside the tympanic membrane), one case of temporary lack of uptake by taste buds, and one case of strange sensation on the tongue (i.e., ageusia).

Device Failures

50 subjects were implanted with the Neuro Zti cochlear implant. All implants remained fully functional during the entire study period.

2. Effectiveness Results

The analysis of device effectiveness was based on the previously defined primary and secondary effectiveness endpoints. Thirty-three (33) of 34 native English-speaking subjects, from the FAS cohort, had HINT in quiet scores available pre- and post-operatively. Key effectiveness outcomes are presented in **Table 10** and **Table 11**.

Primary Effectiveness Endpoint

The primary effectiveness endpoint with the Neuro Cochlear Implant System was defined for the English-speaking participants as the difference between scores obtained for HINT-Q at 6 months post-activation with their cochlear implant alone and pre-operative best-aided scores. The success criterion for the primary effectiveness endpoint was defined as a clinical benefit at 6 months of 20%. The average clinical benefit at 6 months for HINT-Q was 51.5%. The one-sided, one-sample t-test gives a significant p-value: $t(32) = 5.5$, $p < .001$. The null hypothesis is rejected, indicating that the mean clinical benefit at 6 months for HINT-Q met the pre-defined success criterion (i.e., greater than the clinical benefit of 20%) (see shaded cell in **Table 10**). Therefore, the primary effectiveness endpoint was met.

Secondary Effectiveness Endpoint

The secondary effectiveness endpoints with the NCIS were defined for the English-speaking participants as 1) the difference between HINT-Q obtained at 3 and 12 months post-activation with their cochlear implant alone and pre-operative, best-aided scores; and 2) the difference between HINT-N scores obtained at 3, 6, and 12 months post-activation with their cochlear implant alone and pre-operative, best-aided scores. As shown in **Table 10**, on average, the study subjects showed improved scores in both HINT-Q and HINT-N over time. Therefore, the secondary effectiveness endpoints were met.

Table 10: Speech Scores in Percent (%) Correct (English-Speaking FAS Population, 34 Subjects). Shaded cell corresponds to primary effectiveness endpoint of the study.

HINT Score	Mean ± Standard Deviation (SD) [median] [min; max] English Speaking Subjects N=34			
Test Conditions	Test session			
	Pre-operative baseline	3-months post activation	6-months post activation	12-months post activation
	Best aided	Cochlear Implant ear only		
HINT Sentences in Quiet (60 dB SPL)	13.3 ± 16.0 [4.0] [0.0 ; 50.1]	55.8 ± 31.8 [56.1] [0.0 ; 99.1]	64.8 ± 27.2 [64.0] [9.6 ; 98.6]	70.1 ± 24.5 [74.1] [5.6 ; 97.6]
Average clinical benefit (Follow-up minus pre-operative score). Statistical significance at 6 months.	-	42.4 ± 38.3 [46.6] [-50.1 ; 96.4]	51.5 ± 33.8 [59.7] [-40.5 ; 98.6] ***p* < .001**	56.7 ± 30.3 [62.2] [-17.1 ; 96.7]
HINT Sentences in Noise (+10 dB SNR)	13.3 ± 17.7 [3.3] [0.0 ; 52.8]	43.8 ± 30.6 [42.8] [0.0 ; 93.7]	52.3 ± 30.0 [47.7] [0.0 ; 93.4]	57.6 ± 29.9 [57.9] [0.0 ; 97.7]
Average clinical benefit (Follow-up minus pre-operative score)	-	30.5 ± 34.7 [33.9] [-31.9 ; 90.4]	39.1 ± 33.4 [40.0] [-31.9 ; 93.4]	44.3 ± 33.9 [46] [-10 ; 97.7]

3. Subgroup Analyses

Effectiveness Data Stratified by Performance

Table 11 displays the proportion of subjects who performed poorer, similar, and better in the cochlear implant alone condition for each the primary and secondary effectiveness endpoints, when compared to the pre-operative, best-aided baseline condition.

In order to obtain details about the distribution of clinical benefit among the clinical study sample, a positive difference between post-implant and pre-implant

scores exceeding 10 percentage points (pp) was adopted as the cutoff values for an improvement ("better" category). Similarly, a decrease between pre- and post-implant scores that exceeded 10 pp was adopted as the cutoff value for a worsening ("worse" category)). A difference between pre- and post-implant scores of less than 10 pp was adopted as the cutoff value for no change in performance. Results of this analysis are displayed in **Table 11**.

Over 82% of the subjects exhibited similar or better performance on both endpoints. Specifically, over 94% of the subjects exhibited similar or better performance on HINT-Q and HINT-N at 12-month interval compared to pre-operative baseline. Of note, however, there were small proportions of subjects who performed poorer for HINT-Q accuracy (1 out 34 subjects (2.9%)) and HINT-N accuracy (3 out of 34 subjects (8.8%)), respectively, at the 6-month interval compared to pre-operative baseline. The poor performance for these four cases may have been due to a depression episode, issue with a sound processor (which was later exchanged), and in the case of two subjects, older age compared to the average age in the study population. As noted above, one subject could not be assessed at follow-up intervals and is referred to as "unknown" in **Table 11**.

Table 11: Clinical Benefit for the 34 English-speaking FAS Participants

	3 months	6 months	12 months
HINT Sentences in Quiet (60 dB SPL)			
Better (> 10 pp)	76.5% (n=26)	85.3% (n=29)	88.2% (n=30)
Similar (-10 to 10 pp)	5.9% (n=2)	8.8% (n=3)	5.9% (n=2)
Worse (< -10 pp)	14.7% (n=5)	2.9% (n=1)	2.9% (n=1)
Unknown (not measured)[ǂ]	2.9% (n=1)	2.9% (n=1)	2.9% (n=1)
HINT Sentences in Noise (+10 dB SNR)			
Better (> 10 pp)	64.7% (n=22)	70.6% (n=24)	79.4% (n=27)
Similar (-10 to 10 pp)	20.6% (n=7)	17.6% (n=6)	17.6% (n=6)

Worse (< -10 pp)	11.8% (n=4)	8.8% (n=3)	0.0% (n=0)
Unknown (not measured)[ǂ]	2.9% (n=1)	2.9% (n=1)	2.9% (n=1)

[ǂ]*One subject from FAS completed HINT at baseline, but did not complete it at follow-up visits. The data is missing at random and was not included in the analysis. Omitting this data does not affect the statistical validity of the results.*

Other effectiveness measures and analyses

Effect of baseline characteristics on endpoints: Post hoc analyses were conducted to determine which, if any, of the six baseline variables (pre-operative PTA, pre-operative HINT scores, age, duration of hearing loss of any degree, duration of severe-to-profound hearing loss, and duration of hearing aid use) affected outcome(s). Multivariate analyses revealed that four baseline characteristics (pre-operative HINT scores, age at implantation, duration of hearing loss, and duration of severe-to-profound hearing loss) were each negatively associated with HINT-Q. The inference from these analyses is that a better pre-operative speech score, earlier age at implantation, and/or a shorter duration of hearing loss is associated with better effectiveness performance.

Analysis by study site: The consistency of the primary effectiveness endpoint was examined across investigational sites by testing for an effect of site in an ANOVA model, based on 34 English-speaking subjects who completed the 6-month speech recognition tests. The results indicated no evidence of site effects on the primary effectiveness endpoint.

4. Pediatric Extrapolation

The NCIS is indicated for patients 18 years and older as proposed by the applicant. The youngest subject in the pivotal study was 38 years old. The physical and psychological differences between an individual aged 18 to 21 years old (a pediatric adolescent age range per FDA definition), and an individual aged 22 years and older (adult age range per FDA definition) for the NCIS, are not considered significant. See the guidance available at the following link for further information on premarket assessment of pediatric medical devices: https://www.fda.gov/media/73510/download. Therefore the pivotal study data are

considered supportive for the entire indicated age range of individuals 18 years and older, including the 18 to 21 year old indicated pediatric subpopulation.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 6 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Literature Search Strategy

The company conducted an extensive literature search, according to PRISMA statement [6], to collect additional supporting clinical evidence of cochlear implants in patients 18 years of age and older, with severe-to-profound sensorineural hearing loss indications. The search terms used, and results are listed in **Table 12** to **Table 14**.

Table 12: Search Terms and Results

Search topic	Search terms	Query	Results
Effectiveness Searches			
1.	Cochlear Implant AND HINT	('cochlear implant'/exp OR 'cochlear implant') AND hint AND [humans]/lim AND [english]/lim AND [abstracts]/lim AND	80

		[clinical study]/lim AND [2000-2020]/py	
Search topic	**Search terms**	**Query**	**Results**
Safety Searches			
2.	Cochlear Implant AND (complication OR adverse event OR failure OR risk OR surgical safety)	cochlear AND implant AND ((complication OR adverse) AND event OR failure OR reimplant OR risk OR surgical) AND safety AND [humans]/lim AND [english]/lim AND [abstracts]/lim AND [clinical study]/lim AND [2010-2020]/py	119
		Total references	259
		Duplicates	17
		Total references after removal of duplicates	242

Table 13: Inclusion and Exclusion Criteria

Inclusion Criteria	
	Reference is a clinical study
	Reference has clinical data on unilateral use of cochlear implants
	Reference has clinical data on post-lingual adult human populations
	Reference has clinical data from subjects with double-sided deafness
	Reference has clinical data from subjects with no known contraindications has clinical data on safety and/or effectiveness of cochlear implants
	Reference has performance outcomes that include HINT sentence scores

	Reference is clinical study with high-quality design and appropriate sample size (>20) per study group
	Reference includes clinical data on pre-surgical scores
	Reference includes clinical data on post-surgical scores reported using CIS alone
	Reference includes clinical data measured at time points of 3-, 6-, or 12- month post-op
	Reference has clinical data from studies where speech test was conducted in free-field condition at an intensity of 60 dB SPL(+/- 5 dB SPLtolerance) in quiet and at a +10dB SNR in noise
	Reference is in English
	Reference was published after 2000
	Reference has abstract
Exclusion Criteria	
C	References discussing patients with obstacle to full electrode insertion
C	References discussing patients with central auditory lesions
C	References discussing patients not fluent in local language
C	References discussing patients with middle ear disease, lesion of auditory nerve, otosclerosis, or cochlear malformation
N	References not discussing cochlear implants
N	References focusing different type of hearing aid
M	Clinical study with sub-optimal design (e.g., LoE below IIIb[1])
M	Sample size inadequate (<20) per study group
T	Reference is meta-analysis, systematic review, clinical guideline, or letter/editorial
T	Study is not clinical in nature (e.g., simulation study, non-clinical study, socio-economic study, etc.)
T	Study does not focus on device (e.g., may focus on technique, procedural aspects, etc.)
L	References in languages other than English
D	References duplicate
OS	References out of scope of the review (e.g., different medical field, different condition, different anatomical sites, etc.)

OS	References out of scope of the review (e.g., different clinical outcome measured, etc.)

Exclusion Code; C: Probable Contraindication, N: Not Relevant device, M: Methods Not robust, T: Type of Publication not appropriate, L:Language; D: Duplicate, OS: Out of Scope.

Table 14: Literature Scientific Validity of the Individual Clinical Data: LoE of the Publication

Level of Evidence		Clinical Study Type
MA/SR		Evidence obtained from meta-analysis or systematic review
I	Ia	Evidence obtained from properly designed randomized and controlled clinical study
	Ib[2]	Evidence obtained from pseudo-randomized controlled studies, randomized controlled studies with limitation
II	IIa	Evidence obtained from not randomized prospective studies comparative with current control
	IIb	Evidence obtained from not randomized prospective studies comparative with historical control
	IIc	Evidence obtained from non-comparative prospective studies
III	IIIa	Retrospective study, consecutive patients
	IIIb	Retrospective study, not consecutive patients
IV		Evidence obtained from case report
V		Data presented from poster, abstract or conference

Published Literature

Published Literature on the NCIS

The literature search yielded two peer-reviewed papers mentioning the Neuro Cochlear Implant System. Schramm et al, (2020) [7], reported HINT scores and safety results of the OUS pivotal study as described above.

Franco-Vidal et al. (2020) [8] reported on the speech recognition outcomes of the Neuro 2 sound processor upgrade in a prospectively designed, clinical study. In this study, potential changes in speech identification and patient satisfaction related to the upgrade from the Neuro One to the Neuro 2 sound processor were examined. Patients included 44 adults and 26 children with severe-to-profound hearing loss who were all using a Neuro Cochlear Implant System for at least five months. Patients were upgraded with the new Neuro 2 sound processor and tested for speech perception before and after upgrade and tested again after a three-month period of acclimatization to Neuro 2. Speech perception (in quiet) was tested using a French open-set monosyllabic word identification test (Lafon test), a test similar to the CNC words test used in the United States. Speech identification scores were 58.3% ± 22.7% with Neuro One increasing to 67.4% ± 19.3% with Neuro 2 after 3 months of acclimatization. The increase in scores was attributed to fine-tuning occurring at the upgrade visit and to the natural course of improvements after cochlear implant activation, participants still being in their improvement period. Satisfaction questionnaires showed an improvement from Neuro One to Neuro 2 sound processors, which was mostly associated with the new, more compact and lighter design and to the availability of rechargeable batteries.

Published Literature on Adult Cochlear Implant Users with Severe-to-Profound Hearing Loss

Three studies published in the scientific literature presented sufficient similarities in terms of patient indication criteria, device use, test conditions (HINT sentences and pre-op in best aided vs. post-op in the CI ear only) and follow-up at 3-, 6-, and 12-month intervals. This permitted direct comparisons between the study findings from the OUS pivotal study described above and the results reported in Schramm et al., 2020 [7]. The reviewed articles were Balkany, 2007 [9] (55 patients); Buchman, 2014 [10] (13 patients) and Massa, 2014 [11] (130 patients). They included users of cochlear implant systems from the three other manufacturers. A statistical analysis performed on the reported HINT scores in quiet allowed an estimate of the change from baseline to six months in these studies, and was reported to be 59.2 percentage points.

Published Literature on Safety of Cochlear Implant Systems in Adults

A literature search on surgical safety in cochlear implant procedures led to a total of 35 references selected for review. After analysis, among these 35 references, 6 reported sufficiently detailed data on major surgical complication and 3 reported minor complication rates (see **Table 15** and **Table 16** below for results). All complication rates use the number of patients as the denominator. It should be noted that there is a general field consensus regarding the definition and documentation of major complications (corresponding to the definition used in the pivotal study: events requiring additional surgical intervention and/or hospitalization for treatment), However, minor adverse events are not consistently or clearly defined in the literature. **Table 16** below presents device and procedure related adverse event data that could be retrieved from the literature.

Major post-surgical complications

Table 15 below displays the reported major complication rate from 6 articles, totaling 1,316 patients who underwent cochlear implant surgery. The weighted average rate of major complications was 4.2%, varying from 1.7% in Hansen et al., 2010 [16] to 8.6% in Jeppesen et al. 2013 [12]. Regarding the primary safety endpoint of the present study, 2 major complications were reported, leading to an incidence rate of major complications during the study of 3.9%. A statistical comparison between the major complication rate of the present study and the literature was not conducted.

Table 15: Major Complication Rates from Literature

Reference	N (Adults)	Median or average Age at implantation	Retrospective study range or Prospective	Major Complication Rate (% patients)
Farinetti et al., 2014 [15]	168	51.9	1993-2013	6.0%
Hansen et al., 2010 [16]	180	48.5	1982-2007	1.7%
Jeppesen et al., 2013 [12]	269	52.0	1994-2010	8.6%
Kuzovkov et al., 2016 [17]	24	NA	Prospective	3.0%
Petersen et al., 2018 [14]	463	NA	1995-2016	1.9%
Stamatiou et al., 2011 [13]	212	47.5	1986-2010	4.7%
Weighted average	-	49.8	-	**4.2%**
Current Study	51 (SAS)	69.5	Prospective	3.9%

Minor post-surgical complications

Table 16 below lists the observed minor complication rate from 3 articles, totaling 617 adult patients. The weighted average rate of patients experiencing minor complications was 47.8%. Regarding the primary safety endpoint of the pivotal study, the patient incidence rate of all minor complications during the study was 47.1%, among which 39.2% were procedure- or device-related, both values being below the weighted average from literature (albeit no statistical comparison was conducted).

Table 16: Literature review on Minor Complication Rates

Reference	N (Adult cases)	Retrospective study range	Minor Complication Rate (% patients)
Farinetti et al. 2014 [15]	168	1993-2013	21.4%
Hansen et al., 2010 [16]	180	1982-2007	55.6%
Jeppesen et al., 2013 [12]	269	1994-2010	59.0%
Weighted average			**47.8%**
Current study			47.1%

Published Literature on Sound Processing Strategies

The applicant conducted a literature search to collect data supporting performance and safety of these sound processing strategies. The literature search yielded 5 peer-reviewed articles that reported data regarding sound processing strategies. The results are listed in Table 17. The full references for these articles in table are included in the references section at the end of this document.

Studies included patients aged 18 years and older implanted with legacy Oticon Medical devices (Digisonic implant with Saphyr sound processor) and with the Oticon Medical NCIS (Neuro Zti implant with Neuro One or Neuro 2 sound processor).

Table 17: Speech scores in Percent (%) correct (Literature search)

				Word recognition [Signal level, in dB] Mean±Standard Deviation (SD)		Sentence recognition Mean±Standard Deviation (SD)	
Study	**Cochlear Implant System** Implant/ Sound processor	**Signal processing**	**N Subjects**	**Quiet**	**Noise**	**Quiet**	**Noise**
Lazard et al. 2010 [18]	Digisonic/ Saphyr	MPIS (XDP)	55	65 dB HL 68.0 ± 30.0	N.A.	65 dB HL 75.0 ± 20.0	N.A.
Borger et al. 2015 [19]	Digisonic/ Saphyr	MPIS (XDP)	10	65 dB HL 78.0 ± 12.3	+10 dB SNR 52.0 ± 19.3	65 dB HL 94.0 ± 7.8	N.A.
Bozorg et al. 2016 [20]	Digisonic/ Saphyr	Crystalis (XDP)	20	70 dB SPL 80.0 ± 22.0	+10 dB SNR 59.0 ± 22.3	N.A.	N.A.
Schramm et al. 2020 [7]	Neuro Zti/ Neuro 2	Crystalis (CAP)	18	N.A.	N.A.	60 dB HL 72 ± 23.5	+10 dB SNR 54 ± 29.7
Franco-Vidal et al. 2020 [8]	Neuro Zti/ Neuro One	Crystalis (CAP)	41	65 dB SPL 68 ± 24	+10 dB SNR 58 ± 24	N.A.	N.A.

Note: factors such as test setup, listening material, patient etiology and age groups are not matched between the different studies so any valid comparison between studies remains difficult.

Speech outcomes in this study were assessed with Crystalis CAP and results presented in [7] Crystalis XDP, MPIS XDP and MPIS CAP (not studied) are

available in legacy devices and extensive experience was acquired over the past 10 years.

Regarding the compression strategy, both XDP and CAP aimed to maximize the information transfer for a given presentation level (XDP) or dynamically adapt to the environment (CAP). When the signal processing was modified (XDP vs. CAP), no effect was observed on speech performance. This is confirmed in studies [20] and [8], showing 59% and 58% word recognition in noise, respectively. The speech recognition performance in quiet 80% and 68% [8, 18, 20], is also consistent with the reported outcomes among the cochlear implant recipients in the existing literature at the same range of sound intensity [21,22]. Thus, the applicant believes that MPIS XDP data is applicable to support the MPIS CAP strategy.

Regarding the performance from channel selection strategy, MPIS and Crystalis, results from all studies indicate acceptable word and sentence recognition in quiet and in noise, all beyond 50%. As expected, performance decreases when the subjects are placed under a noisy environment. The noise was fixed at 10 dB below the speech (i.e., 10 dB SNR). At this level, as shown in studies [7,8,19,20], subjects were able to recognize either words or sentences in noise with similar scores, between 52% to 59%.

These data support that the patient performance is acceptable for MPIS XDP, Crystalis XDP and Crystalis CAP.

None of the studies reported any safety issue relating to the sound processing strategies.

Limitations

Limitations of the literature data as RWE include: 1) relatively short follow-up duration, 2) variability across patients in rehabilitation procedures and cochlear implant settings, 3) halting of study enrollment due to provisional statistical results, 4) test choice performed at the discretion of the audiologist due to retrospective study design, 5) uncontrolled parameters, limited duration of

listening with the implanted ear, and low power of study design, 6) lack of details regarding study endpoints, eligibility criteria, adverse event collection, statistical method, and individual data, 7) incomplete reporting, particularly of measures of variability such as standard deviation, 8) different study designs (e.g. randomized controlled trials, retrospective case series, and post-hoc analyses), and 9) lack of consistency in study outcomes. All the above limitations precludes pooling data from different studies for random-effects meta-analysis, which adjusts the weight assigned to each study and the confidence interval calculation to account for more variability in results than expected due to sampling error alone. However, given that all subjects in the above articles identified through the literature search have bilateral severe to profound hearing loss (PTA $\geq$ 70 dB HL) in the ear to be implanted and, therefore, match the proposed candidacy criterion for cochlear implantation among patients aged 18 years and older, with bilateral severe-to-profound sensorineural hearing loss, the safety and effectiveness data reported in these articles can serve as supporting evidence to confirm the findings captured in the pivotal study according to FDA guidance document titled "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices" (issued August 31, 2017).

Conclusions

This literature based clinical evaluation provides support for the safety and effectiveness of NCIS indicated for individuals 18 years of age and older, with a bilateral severe-to-profound hearing loss who obtain limited benefit from hearing aids. Overall, the safety and effectiveness profile of the NCIS captured in the pivotal study is consistent with the clinical outcomes in the literature reports for approved cochlear implant systems.

This literature review also provides supporting evidence regarding the audiological equivalence of Neuro One and Neuro 2 sound processor. In addition, the literature search on speech recognition outcomes with the various possible sound coding strategies supports a reasonable assurance of device performance (safety and effectiveness). The speech recognition performance in the literature reports for patients fitted with Crystalis XDP and MPIS XDP appears comparable to speech outcomes of pivotal study subjects using Crystalis CAP.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Ear, Nose, and Throat Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

Primary and secondary effectiveness endpoints were defined. For both endpoints, post-implant performance was compared to pre-operative baseline. Performance was measured unilaterally, i.e., using the NCIS alone and compared to the preoperative, best aided baseline condition. The primary and secondary effectiveness endpoints were defined as a mean improvement in HINT-Q and HINT-N scores, respectively.

Primary and Secondary Effectiveness Endpoint Results: Statistically significant improvements in mean HINT-Q score occurred from the pre-operative, best-aided baseline to the 6-month post activation with cochlear implant alone condition. Numerical score increases also occurred 1) in mean HINT-Q from the pre-operative, best-aided baseline to the 3- and 12-month post activation with cochlear implant alone condition; and 2) in mean HINT-N from the pre-operative, best-aided baseline to the 6- and 12-month post activation with cochlear implant alone condition. It was thus concluded that both primary and secondary endpoints were met.

In addition, over 82% of the subjects exhibited similar or better performance on both HINT-Q and HINT-N endpoints. Specifically, over 94% of the subjects exhibited similar or better performance on HINT-Q and HINT-N at 12-month interval compared to pre-operative baseline.

B. Safety Conclusions

The risks of the device are based on data collected in the OUS clinical study conducted to support PMA approval as described above. The primary safety

objective was to report all complications/adverse events (major or minor complications) as the number and proportion of individuals experiencing an adverse event.

The major complication incidence rate was 3.9%, including one (1) tinnitus event, possibly related to the device and one (1) chronic bronchitis requiring hospitalization, possibly related to the study procedure. The study-related minor complication rate was 39.2%. The observed major and minor complications were consistent with those seen in approved cochlear implant systems.

No device-related severe adverse events, device failure, or explantation were observed.

The long-term safety and effectiveness of the NCIS is yet to be determined. The post approval study (PAS), which is specified in the approval order is designed to assess the time course of adverse events and speech performance. Based on the results of this PAS, the labeling for the NICS will be updated accordingly.

C. Benefit-Risk Determination

The probable benefits of the device are primarily based on data collected in the clinical study conducted to support PMA approval as described above. The clinical study results for the NCIS demonstrated a statistically and clinically significant benefit from use of the NCIS at the post-operative intervals in speech recognition performance over the pre-operative, best aided performance. Over 82% of the subjects exhibited similar or better performance on both effectiveness endpoints (primary and secondary endpoints across the 3, 6, and 12 month follow up time points). Moreover, over 94% of the subjects exhibited similar or better performance on HINT-Q and HINT-N at 12-month interval compared to pre-operative baseline. Therefore, the NCIS is expected to improve speech recognition (in terms of HINT-Q and HINT-N) for a majority of the indicated population.

The probable risks of the device are also based on data collected in the clinical study conducted to support PMA approval as described above. The safety data from the OUS clinical study suggest that the subjects tolerated the risks well, especially since the majority of adverse events were device/procedure related to cochlear implantation surgery and resolved postoperatively. The observed major

and minor complications/adverse events were consistent with those seen with approved cochlear implant systems.

Additional factors considered in determining probable risks and benefits for the NCIS device included:

1. Patient Perspective

This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the PMA for this device.

In conclusion, given the available information above, the data support that the overall benefits of the NCIS outweigh the risks for patients who do not benefit from traditional hearing aids and who meet the criteria specified in the proposed indications for use.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The provided preclinical testing for the device was acceptable. Based on the OUS clinical study results, it is reasonable to expect clinical benefits with use of the NCIS in terms of improvement in speech understanding in quiet and noise since the average performance of the study population showed statistically significant improvement in the primary effectiveness endpoint measure, and the secondary endpoint measures were also met. The risks associated with implanting the NCIS are comparable to those seen with approved cochlear implant systems. FDA believes that the available data demonstrate that the benefits outweigh the risks in the pivotal study subject population, particularly since the device provided benefit for most subjects.

XIV. CDRH DECISION

CDRH issued an approval order on June 23, 2021: The final clinical conditions of approval cited in the approval order are described below.

New Enrollment Study: The purpose of this study is to provide longer-term data on the safety and effectiveness of the Neuro Cochlear Implant System under general conditions of use in the post market environment. This study will be conducted as a prospective, non-controlled, non-randomized study in 10 clinical sites. A total of 60 subjects newly treated will be enrolled. Study subjects will be followed for 3 years post implantation of the device with a target follow-up rate of 80% at the end of the study. The primary safety endpoint is the comparison of the type and frequency of adverse events and serious adverse events observed during the study period. The effectiveness endpoints will include the within-subject differences for the two speech recognition tests, i.e., word recognition in quiet as evaluated with the Consonant-Nucleus-Consonant (CNC) test, and sentence recognition as evaluated with the AzBio test. Follow-up will occur at 1-month post-implantation and 3-, 6-, 12-, 18-, 24-, and 36-months post-activation. Every explanted device will be tested and assessed to determine the reason for explantation and all device explantations will be reported as serious adverse events.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

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