SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Hybrid Cochlear Implant

Device Trade Name: Nucleus® Hybrid™ L24 Cochlear Implant System, consisting of:

- CI24REH Cochlear Implant
- Nucleus 6 Sound Processor (CP910 or CP920) with Acoustic Component, cable, and coil; Accessories, including CR200 Series Remote Assistants (CR210 or CR230 for patient use, CR220 for intraoperative professional use)
- Custom Sound v4 programming software

Device Procode: PGQ

Applicant's Name and Address: Cochlear Americas
13059 E Peakview Ave.
Centennial, CO 80111

Date(s) of Panel Recommendation: November 8, 2013

Premarket Approval Application (PMA) Number: P130016

Date of FDA Notice of Approval: March 20, 2014

Priority Review: Granted priority review status on June 27, 2013 because the device represents a breakthrough technology.

II. INDICATIONS FOR USE

The Nucleus® Hybrid™ L24 Cochlear Implant System is intended to provide electric stimulation to the mid- to high-frequency region of the cochlea and acoustic amplification to the low frequency regions, for patients with residual low frequency hearing sensitivity. The system is indicated for unilateral use in patients aged 18 years and older who have residual low-frequency hearing sensitivity and severe to profound high-frequency sensorineural hearing loss, and who obtain limited benefit from appropriately fit bilateral hearing aids.

Typical preoperative hearing of candidates ranges from normal to moderate hearing loss in the low frequencies (thresholds no poorer than 60 dB HL up to and including 500 Hz), with severe to profound mid- to high-frequency hearing loss (threshold average of 2000, 3000, and 4000 Hz ≥75 dB HL) in the ear to be implanted, and moderately severe to

profound mid to high-frequency hearing loss (threshold average of 2000, 3000, and 4000 Hz ≥ 60 dB HL) in the contralateral ear.

The CNC word recognition score will be between 10% and 60%, inclusively, in the ear to be implanted in the preoperative aided condition and in the contralateral ear will be equal to or better than that of the ear to be implanted but not more than 80% correct.

Prospective candidates should go through a suitable hearing aid trial, unless already appropriately fit with hearing aids.

III. CONTRAINDICATIONS

The device is contraindicated for individuals who have the following conditions:

1. Deafness due to lesions of the acoustic nerve or central auditory pathway
2. Active middle ear disease, with or without tympanic membrane perforation
3. Absence of cochlear development
4. A duration of severe to profound hearing loss of 30 years or greater

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Nucleus® Hybrid™ L24 Cochlear Implant System labeling.

V. DEVICE DESCRIPTION

A. General Description

The Nucleus® Hybrid™ L24 Cochlear Implant System, which is also referred to throughout this document as the Hybrid L24, is an electric-acoustic stimulation (EAS) cochlear implant system. The Hybrid L24 provides electric (cochlear implant) stimulation to the mid- to high-frequency region of the cochlea and for patients with sufficient levels of residual low-frequency hearing sensitivity postoperatively, also provides acoustic (hearing aid) amplification in low-frequency regions. It consists of both internal and external components, as illustrated in Figure 1.

Figure 1: The Nucleus Hybrid L24 Cochlear Implant System, consisting of the model Hybrid L24 Implant (top), Nucleus 6 Sound Processor with Acoustic Component (bottom left), and two Remote Assistant options, the basic CR210 (bottom middle) or the full function CR230 (bottom right). Illustrations not to scale.

B. Hybrid L24 Implant

The receiver/stimulator assembly and extracochlear electrodes of the Hybrid L24 Implant are identical to those of the marketed Cochlear Nucleus model CI24RE (Freedom™) cochlear implant. However, the intracochlear electrode array of the Hybrid L24 implant is different than the conventional electrode arrays [Straight (ST) and Contour Advance (CA)] used with Cochlear's other models of cochlear implants. While the Hybrid L24 electrode array has 22 active electrodes like Cochlear's conventional electrode arrays, it is shorter and thinner. The goal of this design is to preserve the integrity of the apical region of the cochlea (which mediates low frequencies) and thus increase the possibility of retaining a level of residual low-frequency hearing sensitivity. While conventional, longer electrode arrays marketed by Cochlear typically achieve insertion depths into the cochlea of up to 25 mm (or 420 degrees), the Hybrid L24 electrode array is designed for an insertion depth of up to 16 mm (or 270 degrees).

C. Nucleus® 6 (CP900 series) Sound Processor

The Nucleus® 6 Sound Processor (i.e., CP900 series of sound processor) includes an Acoustic Component that can provide conventional amplification for residual acoustic hearing sensitivity in the lower frequencies. Two versions of the Nucleus 6 sound processor are available: the CP910 and the CP920. These sound processors are identical except that the CP920 has an accessory port for use with accessories.

Both the electric (cochlear implant) and acoustic (hearing aid) sound processing are programmed using Custom Sound Suite software, version 4. Two remote controls are available for patient use: the CR210 basic Remote Assistant and the CR230 fully-featured Remote Assistant. A third remote control is also available only for use by professionals in the operating room, the CR220 Intraoperative Remote Assistant.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

The most common alternative treatment of severe to profound bilateral high-frequency sensorineural hearing loss with residual low-frequency hearing is the use of conventional air conduction hearing aids or, in some cases, frequency transposition hearing aids. Patients may also choose to forego obtaining a hearing device and pursue rehabilitation via speechreading and/or sign language training. Each of these alternatives has its own advantages and disadvantages. A patient should fully discuss the alternatives with his/her physician and audiologist in order to select the treatment that best meets his/her expectations and lifestyle.

VII. MARKETING HISTORY

The Hybrid L24 has been marketed for use in both adults and children in the following countries: Algeria, Argentina, Australia, Belarus, Belgium, Bolivia, Canada, Columbia, Czech Republic, Egypt, Finland, France, Germany, Hong Kong, Hungary, Iran, Israel, Italy, Korea, Malaysia, Netherlands, New Zealand, Norway, Poland, Russian Federation, Saudi Arabia, Singapore, Slovenia, Spain, Sweden, Switzerland, Turkey, and United Kingdom. Since market introduction, approximately 315 Hybrid L24 systems have been implanted worldwide. The Hybrid L24 has not been withdrawn from any market for any reason related to safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of potential adverse effects/complications associated with the implantation and use of the Hybrid L24:

- Sudden losses of residual low-frequency hearing
- Total loss of residual hearing

- Vertigo, dizziness, or balance problems that did not exist preoperatively or worsened postoperatively
- Facial nerve problems including injury and unintended stimulation
- Meningitis
- Perilymphatic fistulae
- Tinnitus that did not exist preoperatively or worsened postoperatively
- Implant Migration/Extrusion
- Skin flap problems
- Device-related problems including programming problems and device failure requiring explantation/reimplantation.

For the specific adverse events that occurred as part of the clinical study, see Section X.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Intracochlear Electrode Array

Table 1 summarizes the preclinical testing conducted for the intracochlear electrode array and lead, including information about the test, purpose, acceptance criteria and results.

Table 1. Intracochlear electrode array and lead testing

Test	Purpose	Acceptance Criteria	Results
Temporal bone insertion	To assess the insertion trauma and performance characteristics of the Hybrid L24 electrode	Verify that the insertion characteristics and insertion safety are acceptable for human implantation in a controlled clinical trial	Electrodes inserted into 18 temporal bones by experienced otologic surgeons using a standard posterior tympanotomy approach. Histological assessment of the temporal bones showed no evidence of trauma. Results also showed minimal resistance when inserting the electrode, full insertion depth could be achieved with a single stroke insertion, and the electrode did not buckle in the proximal region.
Multiple insertion Testing	The electrode array is repeatedly inserted into a model cochlea to ensure sufficient robustness to withstand the forces exerted during manufacture and implantation	Equivalent or better Mechanical and electrical reliability criteria when compared to current approved electrode after 50 insertion and removal cycles	5 Hybrid L24 electrode arrays were tested and passed acceptance criteria
Linear and angular fatigue test of the electrode array	To demonstrate that implant leads have the required resistance to fatigue	Samples must survive 2.5 million cycles while maintaining continuity and showing no visible signs of damage	A total of 12 units were exercised through +/- 30º angular (four units) and +/- 10% of electrode length (eight units) at about 2 cycles per second, in a number of different test planes. All samples met acceptance criteria
Severe stress and twist of the electrode lead	To ensure the electrodes will withstand severe stress caused by stretching, and twisting	Implant must maintain electrical continuity throughout testing process, visual inspection must show no signs of damage	Two electrode leads were stretched by 10% and rotated 360º clockwise and 360º counter-clockwise over 10 cycles. All samples met acceptance criteria

Test	Purpose	Acceptance Criteria	Results
Severe electrode lead shear test	To ensure the electrodes will withstand severe stress caused by shearing	Implant must maintain electrical continuity throughout testing process, visual inspection must show no sign of damage	Two electrodes leads were clamped at a 90º angle to the longitudinal axis of the implant (all four possible orientations were tested). The face of the shear tool was placed perpendicular to the electrode lead at a distance of 1.2 mm from the titanium case. Electrical continuity of the lead was monitored while the shear tool was pushed slowly (0.1mm/s) to the lead. All samples met acceptance criteria

Preclinical Safety Analysis:
Charge density calculations were performed to specify safe stimulus current levels for the Hybrid L24 implant. Taking into account the area and periphery of the smallest electrode surface, charge density calculations were completed to assure safe current stimulation by electrodes in the cochlea.

B. External Components

Mechanical Robustness and Environmental Testing of External Components
Mechanical and environmental testing was conducted on the external components and remote assistants. This testing is summarized in Table 2:

Table 2. Mechanical robustness and environmental testing of CP900 series of sound processor and remote controls

Test	Purpose	Acceptance Criteria	Results
Cold test	To ensure units can withstand ambient temperatures (-40°C ± 3°C) the product has the possibility of experiencing during field use	All devices must show neither mechanical damage nor degradation in electrical functionality after testing	The units were exposed to conditions specified in IEC 60068-2-1 Part 2 Test Ab: Starting Temperature: Ambient; Rate of Change: <1°C/min (Averaged over 5 min); Test Temperature: -40°C ± 3°C for 16 hours. All units met acceptance criteria
Dry heat	To ensure units can withstand ambient temperatures (70°C ± 3°C) the product has the possibility of experiencing during field use	All devices must show neither mechanical damage nor degradation in electrical functionality after testing	The units were exposed to conditions specified in IEC 60068-2-1 Part 2 Test Bb: Starting Temperature: Ambient; Rate of Change: <1°C/min (Averaged over 5 min) worksheet to record rate; Test Temperature: +70°C ± 2°C for 16 hours. All units met acceptance criteria
Thermal cycling	To ensure units can withstand shifts in temperature (-40°C to 70°C at 1°C ± 0.2°C /min) the product has the possibility of experiencing during field use	All devices must show neither mechanical damage nor degradation in electrical functionality after testing	The units were exposed to conditions specified in IEC 60068-2-1 Part 2 Test Nb: Temperature Range: -40°C to 70°C; Rate of Change: 1°C ± 0.2°C/min; Number of Cycles: 2; Exposure Time at Endpoints: 3 hours per cycle. All units met acceptance criteria
Cyclic damp	To ensure units can withstand environmental conditions (55°C ± 2°C, 93±3% RH, then 25°C ± 3°C, 95% RH) the product has the possibility of experiencing during field use	All devices must show neither mechanical damage nor degradation in electrical functionality after testing	Samples were exposed to conditions specified in IEC 60068-2-1 Part 2 Test Dd: 55°C ± 2°C, 93±3% RH, for 12 hours, then 25°C ± 3°C, 95% RH, for 12 hours and repeated for a total of 6 cycles. All samples met acceptance criteria

Test	Purpose	Acceptance Criteria	Results
Low pressure	To ensure units can withstand low pressures (100 hPa ± 5 %) the product has the possibility of experiencing during field use	All devices must show neither mechanical damage nor degradation in electrical functionality after testing	Samples were placed in a pressure chamber set at 100 hPa (7.25 psi) ± 5 % for 1 hour with no significant damage noted. All samples met acceptance criteria
Random vibration	To ensure units can withstand mechanical strain in the form of random vibration (frequency bandwidth of 5 to 150Hz) as could be expected during field use	All devices must show neither mechanical damage nor degradation in electrical functionality after testing	Samples were subjected to random vibration (BS EN 45502-1:1998, Section 23.2 as per IEC 60068-2-64 Ed. 2.0 b:2008, Test Fh) at a frequency bandwidth of 5 to 150 Hz at an accelerated spectral density of $0.1g^2$/Hz for 30 minutes, across three orthogonal planes. All samples met acceptance criteria
Free fall	To ensure unit can sustain rough shocks that could result from a fall, with three drops at 2.0m being the worst case scenario of normal use	All devices must show neither mechanical damage nor degradation in electrical functionality after testing	Samples were subjected to a free fall drop test (EN 45502-2-3:2010, Section 23.1 as per IEC 60068-2-31 Ed. 2.0, 2008-05, Test Ec). The case half of one CP910 Standard Sound Processor cracked during Freefall testing, and the sound processor remained fully functional. All other tested units showed no cracking and remained fully functional
Ingress protection testing (external components only)	To ensure the unit can resist ingress of solid foreign objects (≥1mm), splashing of liquid (50 kPa – 150 kPa), and dust (<75µm)	All units must be free of evidence of ingress of the test material	IP44 testing was conducted per IEC 60529 Ed. 2.1 b:2001. All configurations passed the testing. IP57 testing was conducted using the rechargeable battery pack per IEC 60529 Ed. 2.1 b:2001. All configurations of units passed IP44 and IP57 ingress protection testing

Test	Purpose	Acceptance Criteria	Results
Clamp force	To assess the ability of the earhook to resist a biting action without producing loose parts or sharp points	The biting action shall not produce any sharp parts or points. It also must not sever the ear hook to produce loose parts	External retention components were subjected to a test using a bite test clamp positioned in an Instron force tester. The force was gradually increased from 0 at a rate of 10N per second until the bite force reached 140N, and held for 5 seconds.All samples met acceptance criteria
Overmould strength test	To assess the strength of the overmould on external retention devices	Force required to delamination the soft part of the earhook from the hard part is greater than 30N	Using a test jig and an Instron force tester, the strength of the overmould on external retention devices was analyzed by increasing force using a displacement rate of 1mm per second. Acceptance criteria were met and the maximum force reached during delamination of parts was greater than 30N
Retention tests	To ensure adequate retention strength of the small CI earhook and small snugfit with band	The force required to remove all units must be greater than 22.5N.	Several tests were set up to measure the force it takes to detach retention components. Acceptance criteria were met and the test subject was only detached with a force >22.5N
LED light test	To ensure the LED light of the external sound processor is visible in expected indoor conditions	BTE under test must be visible from a distance equal to or larger than 4m in an office environment, when looking directly at the BTE	A light meter was used to measure sound processor LED alert light levels. Acceptance criteria were met and light levels were maintained between 100 and 1500 lux

Electrical Testing of CP900 series sound processor

Electrical testing was conducted on the CP900 series sound processor. This testing is summarized in Table 3:

Table 3. Electrical testing of CP900 series sound processors

Test	Purpose	Acceptance Criteria	Results
Electrical basic functionality	To assess typical electrical functionality, including button operation, LED function, voltage / current measurements, audio input channels, and audio output measures	Electrical functions perform as intended, and operate within prescribed voltage / current / resistance windows	Verification testing demonstrated that the general electronic hardware of the remote assistants functions in the manner intended. All acceptance criteria have been met.
RF link electrical verification	To verify performance of the RF link between the CP900 processor and Cochlear implant. This includes RF link coverage, RF link efficiency, and RF link data integrity	All link measurements must fall into specified ranges representing worst case conditions	All units tested met acceptance criteria, with a deviation of one test configuration. The fault in this configuration would manifest as intermittency, and is resolvable through reprogramming
Mobile phone compatibility and RF immunity	To verify the compatibility of the CP900 Sound Processor with use in close proximity to hand held mobile phones, DECT wireless phones and other devices that emit RF radiation	All sound processor configuration must meet requirements for user compatibility and immunity levels as defined by ANSI standard C63.19	The units tested complied with all immunity requirements
Radio testing	Demonstrate that the components of the Nucleus 6 system that are radio frequency radiators meet the Radio regulations and standards required in the United States and other countries.	Using configurations that are representative of the typical system usage, show that no harmful interference is caused.	Verification testing demonstrated that the CP900 series sound processor meets the radio regulations (47 CFR Part 15, RSS – 210 issue 8, EN 300 328 as per R&TTE Directive 199/5EC and CEPT/ERC 70-03). Remote assistants function with firmware as intended, no harmful interference is caused.

Test	Purpose	Acceptance Criteria	Results
EMC (Electromagnetic Compatibility)	To verify that the Sound Processor satisfies requirements for electromagnetic compatibility in clinical use	Meet several criteria for both emissions and immunity (see Results column)	Verification testing demonstrated that CP900 Series meets EMC requirements: Radiated Emissions (CISPR 11), Electrostatic Discharge (IEC 61000-4-2), Radiated RF Field (IEC 61000-4-3), Conducted RF Disturbances (IEC 61000-4-6), Power Frequency Magnetic Field (IEC 61000-4-8), and Immunity (EN 45502-2-3 Clause 27.2 and Clause 27.3), Immunity of Hearing Aids to interferences generated by a wireless phone (IEC60118-13:2011)
RF Link Wireless Range	Verify the wireless range between the external sound processor and the internal device, in both microphone and telecoil modes	To deliver appropriate voltage for skin flap thicknesses between 1mm and 10mm	The units tested complied with acceptance criteria and all wireless range requirements

Electrical Testing of Remote Assistants

Electrical testing was also conducted on the various remote assistants. This testing is summarized in Table 4:

Table 4. Electrical testing of remote assistants

Test	Purpose	Acceptance Criteria	Results
Basic functionality (CR210 / CR230)	To verify the electronic hardware of CR200 series Remote Assistants and show compliance of the devices with the relevant system and electrical component requirements	Considered to pass only if all of the discrete/attribute- based measurements for every tested sample achieve a pass.	Verification testing demonstrated that the general electronic hardware of the remote assistants functions in the manner intended. All acceptance criteria have been met.
EMC (Electromagnetic Compatibility: Radiated Emissions) (CR210 / CR230)	To verify that the Remote Assistant satisfies requirements for Radiated Emissions in clinical case.	Meet the Radiated Emission requirements as per CISPR11[E2].	Acceptance criteria were met. Verification testing demonstrated that the remote assistants meet CISPR11[E2].
EMC: Wireless link, immunity to RF (CR220)	To ensure that the CR220 Intraoperative Remote Assistant will operate as intended in an operating room, when subjected to external interference.	While subjected to interference levels: 1. CR220 shall not be permanently damaged 2. The Sound Processor and/or CR220 can power down and be repowered 3. CR220 shall display RF link loss 4. Impedance or NRT measurement shall not automatically resume with the link auto reconnect.	Verification testing demonstrated accordance to IEC61000-4-3 procedure with a 20V/m level to simulate anticipated interference in a surgical operating theatre. The CR220 Intraoperative Remote Assistant complied with immunity requirements and met acceptance criteria.
Wireless Range Verification (CR210 / CR230)	Verify the wireless range between the external sound processor and Remote Assistant.	At least 80% (40 out of 50) command attempts are successful at a distance of 2m (+/- 5cm) at a variety of angles	The remote assistant met acceptance criteria

Test	Purpose	Acceptance Criteria	Results
Radio compliance (CR210 / CR230)	Demonstrate that the components of the Nucleus 6 system that are radio frequency radiators meet the Radio regulations and standards required in the United States and other countries.	Using configurations that are representative of the typical system usage show that no harmful interference is caused.	Remote assistants function with firmware as intended, no harmful interference is caused.

Lithium Ion battery testing for CP900 series sound processor

Battery safety testing was conducted for the two rechargeable lithium ion batteries that are available for the CP900 series sound processor. These two batteries are offered with the Hybrid L24. This testing is summarized in Table 5:

Table 5. Lithium Ion Battery testing

Test	Purpose	Acceptance Criteria	Results
Testing of rechargeable batteries to UL 1642	To validate the standards that the lithium ion battery applies in the following tests:	See subtest acceptance criteria below	Acceptance criteria were met for all UL1642 tests.
UL 1642: Short circuit at room temperature	To test the discharge response of the battery when charged cells had a short circuit	Units did not explode, catch fire, or rupture during testing. The temperature of the cell did not exceed 150°C.	Units did not explode, catch fire, or rupture during testing and the temperature was within acceptable limits.
UL1642: Short Circuit at 55 °C	To test the discharge response of the battery when charged cells had a short circuit in a warm environment	Units did not explode, catch fire, or rupture during testing. The temperature of the cell did not exceed 150°C.	Units did not explode, catch fire, or rupture during testing and the temperature was within acceptable limits.
UL1642: Abnormal Charge	To evaluate the response of the battery when the cells were charged with maximum specified charge voltage and a current limit of three times the specified maximum current.	Units did not explode, catch fire, or rupture during testing.	Units were intact following the testing.

Test	Purpose	Acceptance Criteria	Results
UL1642: Crush	To test the response of the battery cells under an applied force of 13 ±1kN (3000 ±224 pounds).	The samples did not explode or catch fire.	Units sustained some damage, but met acceptance criteria.
UL1642: Impact	To evaluate the response of the cells after a 20 pound weight was dropped from a height of 24 inches onto the sample.	The units did not explode or catch fire.	Units sustained some damage, but met acceptance criteria
UL1642: Shock	To evaluate the response of the cells after exposure to three shocks of equal magnitude.	The units did not explode, catch fire, leak or vent.	Units did not have any weight change, and met acceptance Criteria
UL1642: Vibration	To evaluate the response of the battery cells after exposure to vibration testing on each of three axes for not less than 90 minutes nor more than 100 minutes.	The units did not explode, catch fire, leak or vent.	Units did not have any weight change, and met acceptance criteria
UL1642: Heating	To measure the response of the cells after with an initial temperature of 20 ± 5ºC (68 ±9ºF), increasing to 130 ± 2°C (266 ± 3.6°F).	The units did not explode or catch fire.	Cells did not explode or catch fire in extreme heat.
UL1642: Temperature cycling	To evaluate the response of fully charged cells subject to hot and cold temperatures in succession.	The units did not explode, catch fire, vent, or leak.	Units did not have any weight change, and met acceptance criteria.

Test	Purpose	Acceptance Criteria	Results
UL1642: Projectile	To measure whether the battery would penetrate a metal screen (a single layer of 0.25 mm diameter wire with 16-18 wires per inch in each direction) when heated until the point it exploded.	Units did not penetrate wire screen.	Units did not penetrate the wire screen and met acceptance criteria.
UL1642: Altitude	To evaluate how a fully charged cell would react when stored for 6 hours at an absolute pressure of 11.6 kPa (1.68 PSI) and a temperature of 20 ± 3° C (68 ± 5° F).	The units did not explode, catch fire, vent, or leak.	Units did not have any weight change, and met acceptance criteria.
Testing of rechargeable batteries to IEC 62133	To validate the standards that the lithium ion battery applies in the following tests:	See subtest acceptance criteria below	Acceptance criteria were met for all IEC 62133 tests.
IEC62133: Insulation and wiring	To evaluate the characteristics of insulation and wiring, including: insulation resistance, maximum anticipated current / voltage / temperature requirements, and wiring orientation / integrity	Insulation resistance was evaluated and is greater than 5MΩ, no internal wiring is compromised due to current / voltage / temperature, and internal connections are sufficient despite reasonable foreseeable misuse	Acceptance criteria were met for all tests
IEC62133: Vibration	To evaluate the response of the battery cells after exposure to vibration testing on each of three axes for 90 minutes ± 5 minutes for each mounting position	The units must not explode, catch fire, leak or vent, and measured open circuit voltage must be within anticipated parameters	Units did not have any weight change, and met acceptance criteria
IEC62133: Moulded case stress at high temperature	To assess the moulded case at high ambient temperature of 70°C ± 2°C for seven hours	A lack of physical distortion of the battery casing, or exposure of internal components	No physical distortion of battery casing was present

Test	Purpose	Acceptance Criteria	Results
IEC62133: Temperature cycling	To evaluate resistance to change in temperature (-20°C to 75°C)	A lack of physical distortion of the battery casing, or exposure of internal components, including fire, explosion, or leakage	No physical distortion of battery casing was present, including fire, explosion, or leakage
IEC62133: External short circuit	To evaluate the resistance of battery cells to an external short circuit at 20°C ± 5°C and at 55°C ±5°C	The units must not exceed an external resistance of 100mΩ, and the units must show no leakage, fire, or explosion	Units met acceptance criteria including a lack of leakage, fire, or explosion
IEC62133: Free Fall	To assess the ability of battery cells to resist an impact from a height of 1.0m onto a concrete surface	The units must not explode or catch fire	All units met acceptance criteria
IEC62133: Mechanical Shock (Crash Hazard)	To evaluate the resistance of battery cells to a total of three shocks of equal magnitude applies in three mutually perpendicular directions	A lack of physical failure, including fire, explosion, or leakage	Units met acceptance criteria including a lack of fire, explosion, or leakage

C. Hybrid L24 End to End Acoustic Verification Testing

End-to-end testing including electrical and acoustical verification, acoustical system behavior and listening tests were completed to verify that the Hybrid L24 functions as intended. Some acceptance criteria have not been met. Two issues occur only at a very high sound level and at a specific frequency (750Hz). Both issues are therefore deemed by the applicant to be acceptable for clinical use as they do not impact the safety and effectiveness of the system. Overall, the results demonstrate that the system functions as intended.

D. Biocompatibility

Intracochlear Electrode Array:
All materials used in the Hybrid L24 electrode array are identical to those used in the CI24RE series introcochlear electrode arrays. The manufacturing process is also unchanged, along with the facilities used, such as cleanrooms, sterilization tools, and sealing machines. Given the changes in design have resulted in no change to manufacturing materials, processes, or equipment, biocompatibility testing performed on the CI24RE series implants may be applied to the Hybrid L24 implant and is summarized below:

Cytotoxicity
Cytotoxicity testing was conducted on prior generation implants to ISO10993-5:1999 and any differences with the latest version (ISO 10993-5:2009) were adequately justified.

Sensitization
Sensitization testing was conducted on prior generation implants to ISO 10993-10:1995 and any differences with the latest version (ISO10993-10:2010) were adequately justified.

Irritation or Intracutaneous Reactivity
Intracutaneous Reactivity testing was conducted on prior generation implants to ISO 10993-10:1995 and any differences with the latest version (ISO 10993-10:2010) were adequately justified.

Systemic Toxicity (acute)
System Toxicity testing was conducted on prior generation implants to ISO 10993-11:2006.

Subacute and Subchronic Toxicity
Subacute and Subchronic Toxicity testing was conducted on prior generation implants to ISO 10993-11:2006.

Genotoxicity
Genotoxicity testing was conducted on prior generation implants to ISO 10993-3:1992 and any differences with the latest version (ISO10993-3:2003) were adequately justified.

Implantation
Implantation testing conducted on prior generation implants to ISO 10993-6:1994 and any differences with the latest version (ISO10993-6:2007) were adequately justified.

CP900 External Components and Remote Assistants:
Testing should indicate materials are non-sensitizing, non- irritation, and no toxicity for all materials with some degree of skin contact in the CP900 System. Biological evaluations/tests were conducted according to ISO 10993-5 and ISO 10993-10. No failures were observed. The materials contained within the CP900 system are therefore safe for use.

E. Sterilization

The Hybrid L24 implant has been adopted into Cochlear's validated EtO Sterilization Process according to AAMI TIR28:2009, therefore demonstrating compliance with EN556-1:2001, ISO 11135-1:2007, ETO residual safety per ISO10993-7:2008 and the requirements for medical device packaging per ISO11607-1:2006. Package validation testing is summarized in Table 6.

Table 6. Package validation testing

<table>
<tr><th>Test Name</th><th>Standard Utilized</th><th>Acceptance Criteria</th></tr>
<tr><td>Visual Inspection</td><td>ASTM F1886</td><td>The package has a complete seal per the following table:
<table>
<tr><th>Package Type</th><th>Minimum seal width requirements</th></tr>
<tr><td>Sterile barrier family #1</td><td>Seal Width ≥ 4.9mm</td></tr>
</table>
When using a bench-top illuminated magnifier lamp, there are no cracks, crevices or tracks in any direction in the seal longer than 2mm.
Without magnification, there is no warping or other visual damage to the tray.
There are no irregularities on the inside surfaces of the TYVEK lid, including tears, cracks, holes or fractures.</td></tr>
<tr><td>Peel Strength</td><td>ASTM F88</td><td>The peak force measured for each sample shall be equal to or above 5.5 N.</td></tr>
<tr><td>Dye Penetration</td><td>ASTM F1929</td><td>Visual inspection of the seal region of tested packages shall show no evidence of dye penetration to the opposite side of the seal via a defined channel, indicating the presence of a leakage site.
Evidence of dye penetration through the porous material through general wetting of the surface (wicking) shall not be taken as the indication of the presence of a leakage site.</td></tr>
<tr><td>Burst Strength</td><td>ASTM F1140</td><td>
<table>
<tr><th>Package Component</th><th>Minimum Burst Pressure (kPa) Before Package Failure</th></tr>
<tr><td>Inner</td><td rowspan="2">≥ 3.7 kPa</td></tr>
<tr><td>Outer</td></tr>
</table>
</td></tr>
<tr><td>Creep</td><td>ASTM F1140</td><td>
<table>
<tr><th>Package Component</th><th>Minimum Hold Pressure (kPa) Without Package Failure</th></tr>
<tr><td>Inner / Outer</td><td>75-85% of the lowest burst test value</td></tr>
</table>
</td></tr>
<tr><td>Sterility</td><td>ISO 11737-2:2009</td><td>No Growth</td></tr>
<tr><td>Smudge test</td><td>ASTM F2250</td><td>No smudging shall be visible on any of the samples following the test.</td></tr>
</table>

Shelf Life:

Expiration dating for the Hybrid L24 has been validated through both accelerated aging and real-time aging. Accelerated aging was performed according to ASTM F 1980-2007 to an equivalent of 2.5 years, and real-time aging was performed to one year. Following aging, the test articles were subjected to the tests identified in Table 6 above. As real-time aging results were not available for time points later than 2 years, a shelf life of one year has been established for the device, and will be indicated on the labeling.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant conducted a clinical study to establish reasonable assurance of safety and effectiveness of the Hybrid L24 in subjects 18 years an older in the US under IDE G070191. Data from this clinical study were the basis for the PMA approval decision. In addition, the applicant has conducted two earlier clinical studies outside of the US on the Hybrid L24 which are briefly described below.

Outside US studies of Hybrid L24

In 2005, a study of the Hybrid L24 was initiated by the applicant in Australia at a single site. Thirteen subjects were implanted and one withdrew following device activation due to advancing Alzheimer's disease symptoms. Group mean word recognition scores reportedly improved. Three of the twelve continuing subjects (25%) experienced low-frequency threshold shifts that exceeded 30 dB at 12 months, while the remaining 9 subjects had smaller threshold shifts.

In 2006, the applicant initiated a multicenter study in the European Union to support its application for the CE mark of the Hybrid L24. There were 16 study sites; 66 subjects were enrolled and implanted. While the collection of effectiveness measures (e.g., speech recognition scores, speech reception thresholds) differed across study sites, speech recognition in quiet was tested most commonly tested and improvements in this measure were generally reported. The group mean for the low-frequency threshold average worsened by 15.1 dB at 6 months post-implantation.

A. Study Design

The pivotal study for the Hybrid L24 was conducted under IDE to evaluate the safety and effectiveness of the Hybrid L24 in individuals who demonstrate significant residual low-frequency hearing and profound high-frequency (above 1500 Hz) sensorineural hearing loss.

The study was a prospective, multi-center, one-arm, non-randomized, non-blinded, repeated-measures clinical study. Both objective and subjective performance data were collected. Each subject served as her or his own control so that post-implant performance was compared to each subject's baseline (pre-implant) performance. Fifty subjects were implanted with a Hybrid L24 across 10 investigational sites.

Investigational Sites

The following list identifies the 10 investigational sites (all US sites); the number of subjects enrolled at each site is identified in parentheses:

- Midwest Ear Institute in Kansas City, Missouri (11)
- NYU Medical Center in New York, New York (10)
- Mayo Clinic in Rochester, Minnesota (7)
- Hearts for Hearing in Oklahoma City, Oklahoma (6)
- Northwestern University in Chicago, Illinois (3)
- Ohio State University in Columbus, Ohio (3)
- Rocky Mountain Ear Center in Denver, Colorado (3)
- University of Cincinnati in Cincinnati, Ohio (3)
- University of Iowa in Iowa City, Iowa (3)
- Center for Hearing and Balance in Chesterfield, Missouri (1)

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in G070191 was limited to patients who met the following inclusion criteria:

   - 18 years of age or older at the time of implantation
   - Severe to profound sensorineural hearing loss for frequencies > 1500 Hz (i.e., threshold average at 2000, 3000, & 4000 Hz > 75dB HL). Low-frequency thresholds up to and including 500 Hz should be no poorer than 60 dB HL
   - CNC word recognition score (mean of two lists) between 10% and 60%, inclusive (i.e., 10% < score < 60%), in the ear to be implanted
   - CNC word recognition score in the contralateral ear equal to, or better than, the ear to be implanted but not more than 80%
   - English spoken as a primary language

   Patients were excluded from the study if they met any of the following exclusion criteria:

   - Duration of severe-to-profound hearing loss greater than 30 years
   - Congenital hearing loss (for the purpose of this study, onset prior to 2 years of age)
   - Medical or psychological conditions that contraindicate undergoing surgery
   - Ossification or any other cochlear anomaly that might prevent complete insertion of the electrode array
   - Conductive overlay of 15 dB or greater at two or more frequencies, from 250 to 1000 Hz
   - Hearing loss of neural or central origin
   - Diagnosis of Auditory Neuropathy
   - Active middle ear infection
   - Unrealistic expectations on the part of the subject, regarding the possible benefits, risks, and limitations that are inherent to the surgical procedure(s) and prosthetic devices

- Unwillingness or inability of the candidate to comply with all investigational requirements

2. Follow-up Schedule

This study involved up to nine visits before and after implantation, for about a one-year period. Candidacy testing included medical and audiological evaluations to determine study eligibility. A 2-week hearing aid trial was required for those prospective subjects who were not previous users of hearing aids that were determined as fit appropriately prior to being accepted as a study candidate, which required one or two additional visits. After confirming eligibility, the subject underwent baseline testing. The device was subsequently implanted in one ear in accordance with the subject candidacy criteria. The device was activated following a healing period of 2 to 4 weeks.

The baseline and postoperative measurements are summarized in Table 7. All patients were scheduled to return for follow-up examinations at 3, 6, and 12 months postoperatively. Preoperatively, a baseline evaluation was conducted that included collection of both unaided and hearing-aided threshold measures, and also hearing-aided baseline measures for the two co-primary effectiveness endpoints (CNC words and AzBio sentences). Postoperatively, the objective parameters measured included the effectiveness endpoint measures under various testing conditions (described below Table 8). Adverse events and complications were recorded at all visits.

Table 7: Schedule of study visits[1]

	Baseline Evaluation	Initial Device Activation	3-month Postoperative	6-month Postoperative	12-month Postoperative
Informed Consent	X				
Medical and Hearing History	X				
Verification of Hearing Aid functioning	X		X	X	X
Unaided Hearing Thresholds and Tympanometry	X	X	X	X	X
Aided Audiometric Thresholds	X	X	X*	X*	X*

	Baseline Evaluation	Initial Device Activation	3-month Postoperative	6-month Postoperative	12-month Postoperative
Aided CNC test in quiet	X		X	X	X
Aided AzBio sentences-in-noise test	X		X	X	X
Adaptive SRT in noise	X			X	
Aided UW-CAMP music perception	X			X	
Questionnaires (SSQ, DUQ, MBQ)	X			X	X
Psychophysical Ts and Cs and electrical impedance		X	X	X	X
Adverse event reporting	X	X	X	X	X

[1] Subjects continued to be monitored on a semi-annual basis after the 12-month interval until study closure. *Aided thresholds were only retested if there was a change in unaided hearing sensitivity at that interval compared to the previous interval.

3. Clinical Endpoints

Test Conditions

Five pre- or post-implant test conditions were proposed: Acoustic Alone (acoustic stimulation to the ear to be implanted), Bilateral Acoustic (acoustic stimulation to both ears), Hybrid (simultaneous electric and acoustic stimulation in the implanted ear via the Hybrid L24 including the Acoustic Component), Bimodal (electric stimulation only using the Hybrid L24 minus the Acoustic Component with contralateral acoustic stimulation), and Combined (electric and acoustic stimulation via the Hybrid L24 and contralateral acoustic stimulation).

Postoperatively, there were three major conditions: Hybrid, Bimodal and Combined, which are illustrated in Table 8 below. The Bimodal condition refers to listening via electrical stimulation to implanted ear and acoustic amplification to the other ear, while the Combined condition refers to listening via electrical stimulation to the implanted ear, along with bilateral acoustic amplification. In the applicant's labeling, the results from the Bimodal and Combined conditions were collapsed and these two conditions were collectively referred to as "Everyday Listening". In order to maintain consistency with the applicant's labeling, the

term “Everyday Listening” is similarly adopted in the remainder of this SSED to describe these two test conditions. The term “Everyday Listening” was not defined as part of the test conditions in the applicant’s study protocol.

Table 8: Postoperative Test Conditions

Condition		*Everyday Listening*	
	*Hybrid**	*Bimodal*	*Combined*
Description	Electrical stimulation and acoustic amplification (HA) to the implanted ear	Electrical stimulation to implanted ear and acoustic amplification to the other ear	Acoustic amplification bilaterally, plus electrical stimulation to the implanted ear
			

* For those subjects who developed a profound /total loss of residual low-frequency hearing, the applicant performed testing with the Hybrid L24 without the Acoustic Component (i.e., electric-alone mode) and included these data under the “Hybrid” condition.

Endpoints

Safety Endpoint: The primary safety endpoint was the number and proportion of individuals experiencing an adverse event, defined as any surgical and/or device-related event. The adverse events include anticipated and unanticipated adverse events. The list of anticipated adverse device effects identified by the applicant follows:

1. Sudden changes in residual low-frequency hearing.
2. Total loss of residual hearing.
3. Vertigo, dizziness, or balance problems that did not exist preoperatively or worsened postoperatively.
4. Facial nerve problems.
5. Meningitis.
6. Perilymphatic fistulae.
7. Tinnitus that did not exist preoperatively or worsened postoperatively.
8. Implant Migration/Extrusion.
9. Skin flap problems.
10. Device-related/programming problems.

The applicant did not propose formal statistical hypothesis testing for the safety endpoint.

Co-Primary Effectiveness Endpoints: Two co-primary effectiveness endpoints were proposed: CNC word-recognition scores and AzBio sentence-in-noise scores. The score for each metric was compared across two conditions: the

(baseline) Acoustic Alone condition and the 6-month postactivation Hybrid condition.

Study success was defined as a statistically significant improvement ($\alpha = .05$) in both co-primary endpoint measures. The null hypothesis (H_0) and alternative hypothesis (H_A) were defined as follows:

H_0: Mean improvement ≤ 0.

H_A: Mean improvement > 0.

Each hypothesis was tested using a paired t-test with one-sided significance level of 0.025. If there was significant evidence that the assumptions of the t-test did not hold (i.e., $p<0.05$ from a Shapiro-Wilk test of normality), a Wilcoxon signed rank test was used.

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

Missing 6-month postactivation data were proposed to be imputed using the last observation carried forward (LOCF) approach.

Sample Size

The calculated minimum sample size was 47 subjects, and the final proposed sample size was 50. With the sample size, the study had more than 90% power to detect 18.1% improvement in the mean CNC word scores and 12% improvement in the mean AzBio sentence-in-noise scores. The effect sizes for these endpoints were based on clinical trial data from a previous Hybrid IDE study (G990155).

Secondary Effectiveness Endpoints: Secondary effectiveness endpoints compared 6-month post-operative performance in the Hybrid condition to preoperative (ipsilateral) Acoustic Alone performance. Three secondary endpoints were defined as the proportion of subjects scoring equal to or better on the following measures: CNC words, CNC phonemes, and AzBio sentences. The success criteria was greater than 75% of subjects for each secondary endpoint. No statistical hypothesis testing was proposed for these secondary effectiveness endpoints.

Audiometric Test Methods & Effectiveness Measures

Audiometric Thresholds

Unaided audiometric thresholds were obtained for each ear, with insert earphones, using the standard audiometric technique for pure-tone testing. Aided audiometric thresholds were obtained for each ear in the sound-field using narrow band noise

and the standard audiometric technique with the speakers positioned at 0° azimuth relative to the subject's head. The contralateral ear was masked/plugged during aided testing.

Unaided testing for both ears included air conduction thresholds at 125, 250, 500, 750, 1000, 1500, 2000, 3000, 4000, 6000, and 8000 Hz, and bone conduction thresholds at 125, 250, 500, 750, 1000, 1500, 2000, and 4000 Hz. Aided thresholds were measured at the following frequencies: 250, 500, 750, 1000, 1500, 2000, 3000, 4000, 6000, and 8000 Hz.

The low-frequency hearing threshold was defined as the threshold averaged over the range 125 through 1000 Hz, inclusively, in the implanted ear.

For the purposes of adverse event reporting, any change in the low-frequency hearing threshold that resulted in a profound loss (> 90 dB HL) and possibly also total loss (defined as no measurable hearing at the maximum output of the audiometer) in the implanted ear was considered by the applicant as an anticipated adverse event. All cases of profound/total loss of residual low-frequency hearing were included in the adverse event tabulations and analyses.

Effectiveness Measures

Consonant-Nucleus-Consonant (CNC) Word Recognition Test

The CNC Word Recognition Test (Peterson & Lehiste, 1962) is a psychometrically validated test of open set word recognition to determine speech intelligibility in listeners with hearing impairments. This test is consisted of 10 recorded lists of 50 monosyllabic words. At each test interval, two lists were administered in quiet at 60 dBA in the sound field and scored as percent correct for words and phonemes. Subjects were tested using a configuration where the target speech was presented via a loudspeaker at 0º azimuth.

AzBio Sentences in Noise Test

The AzBio Sentence-in-Noise Test (Spahr et al., 2012) is a psychometrically validated test to assess CI recipients' ability to understand sentences in the presence of background noise. This test consisted of 33 lists of 20 sentences (five sentences from each of two male and two female speakers. At each test interval, two lists of the AzBio sentences were presented at 60 dBA with the competing noise (multi-talker babble) at 55 dBA, to achieve a +5 dB signal-to-noise ratio. Stimuli were presented from a single loudspeaker located at 0º azimuth.

B. Accountability of PMA Cohort

A total of 100 subjects were consented to be evaluated for participation in the study. Of these 100 subjects,

- 22 failed, not meeting study requirements
- 28 were potential candidates, but discontinued participation and did not proceed with implantation. Of these 28:
    - 16 could not secure insurance and withdrew
    - 8 elected to pursue other options (nonsurgical or traditional cochlear implantation). Of these 8:
        - 3 pursued hearing aid amplification
        - 3 were either no longer interested in pursuing a surgical procedure) or had concerns regarding loss of residual hearing,
        - 2 pursued traditional cochlear implantation
    - 4 did not proceed with the surgery because the maximum number of subjects approved for implantation had been met
- The remaining 50 subjects were implanted with the Hybrid L24 implant.

Of the 50 subjects who were enrolled and implanted (all implanted unilaterally), all subjects had their device activated and reached the 3-month postactivation test interval. At the 6-month interval, 49 subjects (98%) completed all effectiveness outcome assessments, while 48 completed the audiometric testing for hearing sensitivity. One subject's data were not obtained since this subject was explanted and reimplanted with a Nucleus 5 cochlear implant between the 3- and 6-month intervals due to profound loss of low-frequency hearing and poor performance at 3-months post-activation. An additional subject completed effectiveness outcome assessments, but did not complete the audiometric testing at the 6-month interval. Of the 49 subjects available at the 12-month interval, 46 subjects were assessed, while three subjects were not evaluated. One subject was explanted and reimplanted with a Nucleus Freedom™ cochlear implant prior to the 12-month interval. The remaining two subjects withdrew prior to reaching the 12-month interval: one subsequent to a diagnosis of pancreatic cancer, and the other due to advancing dementia.

C. Study Population Demographics and Baseline Parameters

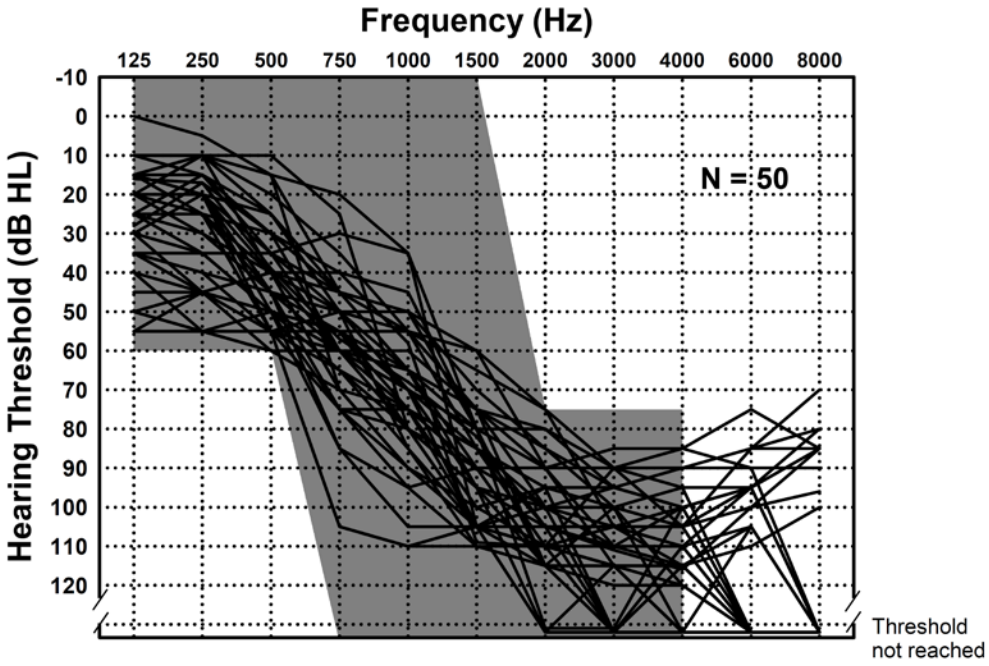
Of the 50 implanted subjects, 25 were female. At the time of implantation, subjects ranged in age from 23 to 86.2 years. The duration of hearing loss (of any degree) ranged from 6 to 84 years. The duration of severe to profound high-frequency hearing loss ranged from 1.6 to 30.1 years. Other subject demographics are summarized in Table 9 below.

Table 9. Descriptive statistics for subject variables

Variable	*Mean*	*SD*	*Min*	*Max*
Age at implantation (years)	64.1	14.7	23.0	86.2
Duration of hearing loss of any degree (years)	28.1	14.9	3.4	73.9
Duration of severe-to-profound high-frequency hearing loss (years)	13.1	7.2	1.6	30.1
Preoperative CNC word score (%)	28.4	14.7	9	64
Preoperative low-frequency hearing sensitivity (from 125-1000 Hz, dB HL)	45.3	10.2	19	63

Figure 2 below shows the preoperative unaided air conduction thresholds in the ear to-be-implanted for all subjects. The shaded region represents the range of audiometric thresholds according to the subject candidacy criteria. Consistent with the study inclusion criteria, hearing thresholds ranged from within normal limits to moderately severe loss up to 500 Hz, sloping downward to severe or profound loss at higher frequencies.

Figure 2. Individual subjects' pre-operative audiograms (curves), audiometric fitting range (gray region).



D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on all 50 implanted patients. The key safety outcomes for this study are presented below in Table 10 through Table 12.

Adverse effects that occurred in the PMA clinical study:

Many of the 10 possible anticipated adverse events (defined earlier) were reported by the applicant to have occurred during the study. In summary, a total of 71 adverse events were reported (see Table 10 below). Of the 50 implanted subjects, 34 (68%) experienced at least one adverse event. Multiple (2-4) adverse events were experienced by 20 of 50 subjects. 24 of 71 adverse events in 23 subjects were unresolved during the study.

Table 10. Number and percentage of adverse events observed for Hybrid L24 subjects.

Event	Number of Events	Percent of Events	Number of Subjects with Event	Percent of Subjects	Percent Resolved
Profound/Total loss of hearing[1]	22	31.0%	22	44.0%	0.0%
Open/short circuited electrodes[2]	11	15.5%	11	22.0%	100.0%
Increased tinnitus	6	8.5%	6	12.0%	100.0%
Tinnitus not present preoperatively	6	8.5%	6	12.0%	100.0%
Explantation/ Reimplantation	6	8.5%	6	12.0%	100.0%
Dizziness	3	4.2%	3	6.0%	100.0%
Dizziness with change in hearing	2	2.8%	2	4.0%	100.0%
Increased tinnitus with change in hearing	2	2.8%	2	4.0%	100.0%
Skin irritation due to externals	2	2.8%	2	4.0%	100.0%
Sound quality issue	2	2.8%	2	4.0%	50.0%
Decrease in performance[3]	1	1.4%	1	2.0%	0.0%
Imbalance	1	1.4%	1	2.0%	100.0%
Imbalance with change in hearing	1	1.4%	1	2.0%	100.0%
Increased impedances with change in hearing	1	1.4%	1	2.0%	100.0%
Local stitch infection	1	1.4%	1	2.0%	100.0%
Overstimulation[2]	1	1.4%	1	2.0%	100.0%

Event	Number of Events	Percent of Events	Number of Subjects with Event	Percent of Subjects	Percent Resolved
Pain in implant ear	1	1.4%	1	2.0%	100.0%
Vertiginous symptoms with change in hearing	1	1.4%	1	2.0%	100.0%
Vertigo	1	1.4%	1	2.0%	100.0%
Total	**71**				

Notes: [1]Although "Sudden changes in residual low-frequency hearing" or "Total loss of residual hearing" were specified in the applicant's protocol, profound/total loss was used as the actual criteria for reporting by applicant. Smaller amounts of hearing loss are discussed below. [2]In terms of the list of adverse effects defined in section VIII, open/short circuited electrodes and overstimulation both fall under device-related/programming problems. [3]Subject explanted/reimplanted with traditional CI on August 26, 2013.

As listed in Table 10, the two most frequently observed adverse events, reported as resolved, were tinnitus-related issues and device-related open shorts experienced by 28% and 22% of subjects, respectively.

In terms of the unresolved adverse events observed in this study, profound/total loss of residual low-frequency hearing was by far the most frequently observed adverse event, occurring in 22 of 50 (44%) of subjects. Six of these subjects were subsequently explanted and reimplanted with a traditional cochlear implant. Loss of residual hearing and device explants are discussed further below.

Loss of residual low-frequency hearing

The proportions of subjects stratified by the amount of low-frequency hearing loss at the 6- and 12-month intervals are summarized in Table 11. The same data, stratified by postoperative residual low-frequency hearing sensitivity, are summarized in Table 12.

Table 11. Proportion of subjects with various amounts of low-frequency hearing loss at 6 and 12 months

Amount of loss in low-frequency hearing (dB)	*6-month (N = 50[1])*	*12-month (N = 46[2])*
≤ 10	24.0% (12/50)	19.9% (9/46)
≤ 20	48.0% (24/50)	45.7% (21/46)
≤ 30	54.0% (27/50)	58.7% (27/46)
> 30	46.0% (23/50)	41.3% (19/46)

[1]Based on the data imputed using LOCF for two subjects with missing data at 6 months.
[2]Based on the data obtained from all subjects evaluated at 12 months.

Table 12. Proportion of subjects' low-frequency hearing sensitivity at 6 and 12 months

Residual low-frequency hearing sensitivity (dB HL)	*6-month (N = 50)*	*12-month (N = 46)*
41 – 55 (Moderate loss)	30.0% (15/50)	32.6% (15/46)
56 – 70 (Moderately severe loss)	18.0% (9/50)	21.7% (10/46)
71 – 90 (Severe loss)	18.0% (9/50)	17.4% (8/46)
> 90 & measurable (Profound)	24.0% (12/50)	17.4% (8/46)
no measurable hearing (Total/Profound loss)	10.0% (5/50)	10.9% (5/46)

As shown across Table 10 and Table 12, profound/total loss of residual low-frequency hearing was experienced by 22 of 50 (44%) of subjects for whom data were available at the time of the PMA submission (i.e., May 30, 2013). Regarding the time course of these losses, 17 subjects experienced the loss by six months post implantation and the remaining five experienced the loss later: one subject by 12 months, two by 18 months, one by 36 months, and one by 48 months. Regarding the amount of loss in their residual low-frequency hearing as of May 30, 2013, 30 of 50 subjects (60%) exhibited more than a 30 dB loss. Five of these subjects' hearing sensitivity later exhibited a loss within 30 dB of preoperative levels as revealed at their most recent follow-up session.

Device Explants

At the time of this PMA submission, 4 subjects were reported to have been explanted and reimplanted. Of the 4 subjects, one subject was explanted and re-implanted between 3 and 6 months post activation, a second subject between 6 and 12 months, and the remaining two subjects after 12 months. The reported reasons for explantation and reimplantation in the first subject included partial electrode shorts, loss of hearing, and poor performance. The three other subjects sought explantation and reimplantation due to hearing loss, poor performance, and dissatisfaction with regards to device outcomes. All four subjects were reimplanted with traditional cochlear implants: one subject was implanted with the CI512 and the other three with the CI24RE. Available preliminary data suggest that performance of these 4 reimplanted subjects is no worse than pre-revision.

On October 24, 2013, the applicant reported that two additional subjects had undergone explantation/reimplantation, both at the end of August 2013. One of these two subjects was initially reported as having profound hearing loss at initial activation and unresolved decreased performance, as discussed earlier. The other subject had improved performance up until 12 months. Following the 12 month period, this subject withdrew from the study; only limited data regarding this subject's pre and post explant performance were provided.

Table 13 summarizes baseline characteristics of the six explanted subjects including age, gender, duration of hearing loss prior to implantation, and pre-

operative low-frequency hearing threshold average. Based on this small sample of explanted subjects, none of these baseline characteristics is observed to be a predictor of the need for explantation/reimplantation.

Table 13. Baseline characteristics of explanted subjects

Age (years)	Gender	Duration of loss prior to implantation (Years)	Etiology of hearing loss	Pre-op low-frequency threshold (dB HL)	Explant/Re-Implant reason
67	Female	42	Unknown etiology	60	Residual hearing loss, partial shorts, poor performance
71	Male	41	Noise exposure	44	Residual hearing loss, dissatisfied
66	Male	15	Ototoxic drugs	43	Residual hearing loss, dissatisfied
81	Female	74	Familial	49	Residual hearing loss, dissatisfied
68	Male	13	Unknown etiology	47	Residual hearing loss
78	Male	38	Unknown etiology	51	Residual hearing loss, decreased performance

Sound quality issues and decreased performance

As shown in Table 10, sound quality issues and decrease performance were reported as unresolved adverse events. Of the two subjects who experienced sound quality issues, in one subject, the event remained unresolved during the study. This subject reported a “static sound” in the presence of speech, at the device programming follow up approximately a month after implantation. Although no receiver/stimulator malfunction was reported per integrity testing

and despite the use of new sound processors and multiple programming sessions, the static sound persisted.

One subject was reported as having experienced decreased hearing performance. This subject had profound loss of residual hearing at initial activation and an additional decrease in electrical hearing performance following the 3-month interval. On October 24, 2013, the applicant reported that this subject has been explanted and re-implanted with a traditional cochlear implant.

2. Effectiveness Results

The analysis of effectiveness was based on the previously defined co-primary and secondary effectiveness endpoints at the 6-month time point. Key effectiveness outcomes are presented in Table 14 through Table 23. Also included below are definitions of the test methods.

Co-Primary Effectiveness Endpoints

As summarized in Table 14, statistically significant improvements in mean CNC word score and mean AzBio sentence-in-noise score occurred from the (Acoustic Alone, hearing-aided) baseline to the 6-month interval postactivation (Hybrid condition). As stated earlier, both measures were conducted on the ipsilateral ear only. Hence, both co-primary effectiveness endpoints were met. These data are based on 49 of 50 (98%) subjects who were assessed at the 6-month interval. When worst-case imputed scores for the missing subject were included in the sample, both co-primary endpoints were still met: the mean improvement with 95% confidence intervals was 35.7% (27.8%, 43.6%) for CNC words and 32.0% (23.6%, 40.4%) for AzBio. These analyses revealed that the results for co-primary endpoints are robust to the missing data.

Table 14. Co-primary effectiveness endpoints results

	Baseline **Mean ± SD (%)**	**6 Month** **Mean ± SD (%)**	**Change** **Mean ± SD (%)**	**95% CI (%)**	***p*-value**
CNC Words	28.4 ± 14.9	65.4 ± 25.4	37.0 ± 26.6	(29.4, 44.6)	< 0.0001
AzBio Sentences in Noise	16.4 ± 14.5	49.2 ± 30.8	32.8 ± 29.1	(24.5, 41.2)	< 0.0001

Secondary Effectiveness Endpoints

Table 15 displays the proportion of subjects who performed poorer, similar, and better in the Hybrid condition for each of the three secondary endpoint metrics at the 6-month interval, when compared to the ipsilateral Acoustic Alone baseline condition. Since over 75% of the subjects exhibited similar or better performance on all three metrics, it was concluded that all secondary endpoints were met. Of note, however, there were small proportions of subjects who performed poorer for CNC word accuracy (4.0%), CNC phoneme accuracy (10.0%), and AzBio score (12.0%), respectively, at the 6-month interval compared to preoperative baseline.

Table 15: Proportion of subjects who performed poorer, similar, or better in the Hybrid versus the (ipsilateral) Acoustic Alone condition at 6 months

Endpoint	*Poorer*	*Similar*	*Better*
CNC Words	4.0% (2/50)	16.0% (8/50)	80.0% (40/50)
CNC Phonemes	10.0% (5/50)	6.0% (3/50)	84.0% (42/50)
AzBio Sentences	12.0% (6/50)	16.0% (8/50)	72.0% (36/50)

Although not prospectively defined in their protocol, the applicant and the FDA also analyzed the secondary endpoints in the bilateral "Everyday Listening" condition (defined under "*Test Conditions"* in Section X.A.3 above) at 6 months and compared with the preoperative Bilateral Acoustic condition (i.e., with two hearing aids). Table 16 displays the proportion of subjects' scoring poorer, similar, or better at 6 months as compared to preoperative baseline. All subjects' scores were similar or better for all three secondary endpoints.

Table 16: Proportion of subjects who performed poorer, similar, or better in the Everyday Listening versus the Bilateral Acoustic condition at 6 months for each secondary endpoint

Endpoint	*Poorer*	*Similar*	*Better*
CNC Words	0% (0/50)	12.0% (6/50)	88.0% (44/50)
CNC Phonemes	0% (0/50)	10.0% (5/50)	90% (45/50)
AzBio Sentences	0% (0/50)	16.0% (8/50)	84% (42/50)

The increase in the proportion of subjects performing similar to or better than baseline in the Everyday Listening (bilateral) versus the Hybrid (unilateral) conditions highlights the importance of the contribution of the residual low-frequency hearing in the non-implanted ear. These results support the unilateral intended use for the Hybrid L24.

3. Subgroup Analyses

Exploration of Effects of Baseline Characteristics on Device Effectiveness

To explore the influence of baseline characteristics on effectiveness outcomes, post hoc simple regression and multivariate analyses were conducted. Simple regression analysis was conducted to assess the effects of baseline characteristics on the co-primary endpoints. For this analysis, each of the two co-primary effectiveness endpoint variables (improvements in CNC Words and AzBio Sentences in Noise) was regressed on each of the six baseline covariates: gender, age at implantation, duration of hearing loss, duration of severe to profound high-frequency hearing loss, baseline CNC word scores, and pre-operative hearing threshold. Multivariate regression analyses were further performed as many of the baseline covariates were correlated. More specifically, three baseline covariates, age at implantation, duration of hearing loss, and gender were correlated. Further, age at implantation and duration and hearing loss were positively correlated.

The six baseline variables (gender, in addition to the five listed in Table 9) were included in the multivariate regression model for all 50 subjects. Among the six covariates, two baseline variables, i.e., duration of hearing loss and pre-operative low-frequency hearing thresholds were observed to be negatively associated with both co-primary endpoints (CNC and AzBio). Table 17 displays the results from this multivariate regression analysis. These results suggest that a shorter duration of hearing loss and/or better pre-operative low-frequency hearing sensitivity may be associated with better effectiveness outcomes.

Table 17. Results from multivariate regression analysis for each co-primary effectiveness endpoint on all six baseline subject characteristics

Subject characteristic	*Improvement in CNC scores*		*Improvement in AzBio scores*	
	Estimate	*p-value*	*Estimate*	*p-value*
Gender (female vs. male)	8.98	0.194	9.05	0.259
Age at implantation (years)	-0.39	0.134	-0.31	0.303
Duration of hearing loss (years)	-0.54	**0.039**	-0.63	**0.038**
Duration of severe hearing loss (years)	0.22	0.634	0.45	0.413
CNC Words (%)	-0.85	**0.001**	-0.34	0.246
Low-frequency hearing threshold (dB HL)	-0.84	**0.023**	-1.08	**0.013**

Device Effectiveness as a Function of Loss of Low-Frequency Hearing

Various post hoc analyses were conducted to examine device effectiveness as a function of subjects' loss of residual low-frequency hearing. In these analyses, all missing 6-month data were imputed with the corresponding 3-month data.

Hearing loss treated as a continuous variable: Simple regression analysis revealed a negative correlation between each co-primary endpoint (improvement in CNC words and improvement AzBio sentences in noise) and loss of residual low-frequency hearing. Loss of low-frequency hearing was analyzed in two ways: by the amount of change of low-frequency thresholds and by the (final) low-frequency hearing sensitivity threshold at 6 months. It was observed that the more low-frequency hearing was preserved, the better the device effectiveness.

Hearing loss treated as a discrete variable: The consistency of the co-primary endpoints based on individual subjects' was further examined post hoc by the residual low-frequency hearing preserved at the 6-month interval. In the analysis presented here, the low-frequency hearing sensitivity at the 6-month interval was divided into the following four ranges: 41 through 55 dB HL (a moderate loss), 56 through 70 dB HL (a moderate-severe loss), 71 through 90 dB HL (a severe loss), and poorer than 90 dB HL (a profound and possibly also total loss). The results are displayed in Table 18 and Table 19.

Table 18: Proportion of subjects who performed poorer, similar, or better for CNC Word Recognition in Hybrid versus Acoustic Alone condition, as a function of residual low-frequency hearing sensitivity at 6 months

Low-frequency hearing sensitivity (dB HL)	*Mean (STD) (%)*	*Proportion of subjects*			
		Poorer	*Similar*	*Better*	*Total*
> 40, ≤ 55	47.3 (22.6)	0% (0/50)	**2% (1/50)**	26% (13/50)	28% (14/50)
> 55, ≤ 70	48.9 (19.2)	0% (0/50)	0% (0/50)	20% (10/50)	20% (10/50)
> 70, ≤ 90	44.1 (19.2)	0% (0/50)	0% (0/50)	18% (9/50)	18% (9/50)
> 90	14.2 (28.0)	**4% (2/50)**	**14% (7/50**)	16% (8/50)	34% (17/50)

Table 19. Proportion of subjects who performed poorer, similar, or better for AzBio Sentence-in-Noise Test in Hybrid versus Acoustic Alone condition, as a function of residual low-frequency hearing sensitivity at 6 months

Low-frequency hearing sensitivity (dB HL)	*Mean (STD) (%)*	*Proportion of subjects*			
		Poorer	*Similar*	*Better*	*Total*
> 40, ≤ 55	45.0 (22.1)	0% (0/50)	**2% (1/50)**	26% (13/50)	28% (14/50)
> 55, ≤ 70	47.5 (25.2)	0% (0/50)	0% (0/50)	20% (10/50)	20% (10/50)
> 70, ≤ 90	41.9 (27.9)	0% (0/50)	**2% (1/50)**	16% (8/50)	18% (9/50)
> 90	7.0 (22.0)	**12% (6/50)**	**12% (6/50)**	10% (5/50)	34% (17/50)

Among those subjects with residual low-frequency hearing sensitivity poorer than 90 dB HL (N = 17), 47.1% (N = 8) performed either similarly or poorer (i.e., did not improve) in both the CNC Word Recognition Test and the AzBio Sentence-in-Noise Test (Table 20).

Table 20: For subjects with residual low-frequency hearing sensitivity thresholds poorer than 90 dB HL, proportions with poorer, similar, or better for CNC Word Recognition scores and AzBio Sentence-in-Noise scores in the Hybrid condition

AzBio / *CNC*	*Poorer*	*Similar*	*Better*	*Total*
Poorer	**11.8% (2/17)**	0% (0/17)	0% (0/17)	11.8% (2/17)
Similar	**17.7% (3/17)**	**17.7% (3/17)**	5.9% (1/17)	41.2% (7/17)
Better	5.9% (1/17)	17.7% (3/17)	23.5% (4/17)	47.1% (8/17)
Total	35.3% (6/17)	35.3% (6/17)	29.4% (5/17)	100% (17/17)

To further investigate the relationship of hearing loss with device effectiveness and evaluate benefit-risk, the applicant conducted post hoc analysis by classifying hearing sensitivity at 6 months into two groups. Group 1 consisted of subjects

whose low-frequency hearing thresholds were better than or equal to 90 dB HL and Group 2 consisted of subjects whose low-frequency hearing thresholds were poorer than 90 dB HL (i.e., profound/total loss of residual low-frequency hearing).

In terms of CNC word recognition scores, the mean of Group 1 is 47% (SD = 20%), which is remarkably higher than the mean of Group 2: 14% (SD = 28%). This suggests that preservation of residual hearing is important for CNC word recognition. Table 21 lists the counts and proportions of subjects whose 6-month scores were poorer than, similar to, or better than the pre-op scores by group. It can be observed that, in Group 1, almost all subjects improved in CNC word recognition performance, whereas, in Group 2, only about half of the subjects did.

Table 21. Improvement in CNC words: Group 1 versus Group 2

	Poorer	**Similar**	**Better**
Group 1 (≤ 90 dB HL)	0/33 (0%)	1/33 (3%)	32/33 (97%)
Group 2 (> 90 dB HL)	2/17 (12%)	7/17 (41%)	8/17 (47%)

The mean AzBio score of Group 1 is 45% (SD = 24%) which is remarkably higher than the corresponding score for Group 2: 7% (SD = 22%). This suggests that preservation of residual hearing is important for AzBio sentence test. Table 22 lists the counts and proportions of subjects whose 6-month AzBio score were poorer than, similar to, or better than the pre-op scores by groups. In Group 1, almost all subjects improved the AzBio test scores, whereas, in Group 2, only about a third of the subjects improved, while a third of subjects performed poorer.

Table 22. Improvement in AzBio sentences: Group 1 versus Group 2

	Poorer	**Similar**	**Better**
Group 1 (≤ 90 dB HL)	0/33 (0%)	2/33 (6%)	31/33 (94%)
Group 2 (> 90 dB HL)	6/17 (35%)	6/17 (35%)	5/17 (30%)

To help characterize device effectiveness in terms of benefit, FDA defined benefit post hoc as improvement on at least one co-primary endpoint test. These data are summarized in Table 23 as proportions out of all 50 subjects.

Table 23. Device Benefit vs. Residual Hearing Preservation (6 mo)

	Benefit	Proportion
Group 1 (≤ 90 dB HL)	Yes	33/50 (66%)
Group 2 (> 90 dB HL)	Yes	9/50 (18%)
	No	8/50 (16%)

For Group 1 subjects, all 33 subjects improved in at least one test. However, for Group 2 subjects, 8 of 17 did not improve in either test: two were poorer in both AzBio and CNC, three were poorer in AzBio with no change in CNC, and three had similar AzBio and CNC scores.

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 10 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

The applicant included test results on the following additional tests in their PMA: SRT in Noise, UW-CAMP, SSQ, DUQ, and MBQ. Results from these tests are briefly summarized below.

Speech Recognition Threshold (SRT) in Noise Test – Significant improvements from the preoperative measurements were reported. Specifically, adding ipsilateral acoustic hearing offered an average of 1.2 dB over contralateral acoustic hearing alone. Bilateral acoustic hearing offered an average SRT advantage of 1.6 dB over contralateral ear alone. Notably, not all subjects completed each test at the 6-month interval: data for this test were only collected from 35 subjects, of whom 30 had some amounts of preserved low-frequency hearing in the implanted ear. In other words, any improvement reported was largely limited to only those subjects with some amounts of residual low-frequency following implantation. The fact that the applicant did not obtain data for the remaining 15 subjects with little or no residual low-frequency hearing makes it difficult to draw any conclusion based on the data set.

The University of Washington Clinical Assessment of Music Perception (UW-CAMP) – The UW-CAMP (Nimmons et al., 2008), a music perception test battery psychometrically validated in adult cochlear implant recipients (Kang, 2009), was adopted to assess subjects' music perception abilities. The UW-CAMP consists of three subtests: pitch discrimination (measured in semitones), melody recognition and perception of timbre (measured in percent correct). The UW-CAMP was administered ipsilaterally and bilaterally at the preoperative baseline and at 6 months. The mean, standard deviation, and number who completed the test are presented in Table 24 for each subtest. The data across all subtests indicate no significant changes between the performance at preoperative baseline and at 6 months for each subset, for both the unilateral and also the bilateral comparisons.

Table 24: Descriptive statistics (Mean ± Standard Deviation)) for UW-CAMP subtests: pitch discrimination, melody and timber identification

Subtest	*Ipsilateral (implanted ear alone)*		*Bilateral (both ears)*	
	Acoustic at baseline	*Hybrid at 6 months*	*Bilateral at baseline*	*Everyday Listening at 6 months*
Pitch (semitone)	1.1 ± 1.0 (N = 50)	1.4 ± 1.5 (N = 46)	1.1 ± 1.1 (N = 50)	1.0 ± 0.8 (N = 46)
Melody (% correct)	66.2 ± 25.7 (N = 50)	65.9 ± 29.5 (N = 47)	66.3 ± 24.8 (N = 47)	66.7 ± 25.0 (N = 46)
Timbre (% correct)	50.8 ± 18.2 (N = 50)	56.6 ± 22.7 (N = 47)	56.2 ± 19.8 (N = 47)	57.0 ± 19.6 (N = 46)

Changes in UW-CAMP subtest scores were also analyzed for the ipsilateral ear only by the two previously defined subgroups: Group 1 (thresholds better than 90 dB HL) and Group 2 (thresholds poorer than or equal to 90 dB HL). The purpose of these additional analyses conducted by FDA was to explore the effects of residual hearing on music perception subtests since acoustical low-frequency hearing is considered important for music perception. Table 25 summarizes the results. Group 2 on average performed more poorly at 6 months compared to baseline in two subtests: pitch discrimination and melody identification. Group 1, by contrast, on average improved in all three subtests, and to a greater extent in timbre recognition than Group 2.

Table 25. Change in UW-CAMP subtest scores (6-month score minus baseline score) for the ipsilateral ear, by subgroup

	Group 1 Change Mean (SD)	Group 2 Change Mean (SD)	Change Difference (Group 1 – Group 2)
Pitch (semitone)	-0.13 (0.92) N=32	1.32 (2.20) N=14	-1.45
Melody (%)	1.7 (10.41) N=32	-10.0 (19.5) N=15	11.7
Timbre (%)	6.8 (19.3) N=32	1.3 (19.2) N=15	5.5

Speech, Spatial, and Qualities of Sound Questionnaire (SSQ) – SSQ includes three hearing domains: (1) hearing for speech in quiet and noisy conditions, (2) spatial hearing, and (3) sound quality. Fifty subjects completed the SSQ preoperatively and 48 completed it at 6 months. Higher scores indicate positive responses. For each subject, the average scores were computed for each hearing domain. Scores for the three subscales were averaged to derive a total score. The comparisons were made between the preoperative baseline and 6-month postoperative time point, as shown in Table 26. The results indicate that the SSQ scores improved at 6 month postoperatively from the preoperative baseline.

Table 26: Descriptive statistics (N, mean, standard deviation) of SSQ at pre-operative baseline and 6-month time point

Subscale	*Pre-operatively*			*6 months*		
	N	*mean*	*std*	*N*	*mean*	*std*
Speech/Hearing	50	3.2	1.3	48	5.4	1.7
Spatial	50	4.5	1.9	48	5.5	1.7
Quality	50	5.0	1.5	48	6.3	1.4
Total	50	4.2	1.3	48	5.7	1.3

Device Use Questionnaire (DUQ) – A total of 48 subjects completed the DUQ at 6 months. The result indicates that, in terms of the preferred way of listening, 65% (34/48) preferred the Combined mode, 29% (14/48) preferred the Bimodal mode, while 6% (3/48) preferred the Hybrid mode. Regarding the "overall satisfaction with their performance with the Hybrid L24 Implant System," 79% (38/48) reported being very satisfied or satisfied, 6% (3/48) reported being neutral, while 15% (7/48) reported being dissatisfied or very dissatisfied. A total of 15 subjects with profound loss of hearing completed the DUQ. Regarding satisfaction "with their performance using their preferred way of listening", among these 15 subjects, 80% (12) reported being very dissatisfied or

dissatisfied, 7% (1/15) reported being neutral, while 13% (2/15) reported being satisfied or very satisfied.

Musical Background Questionnaire (MBQ) – This questionnaire was adopted to examine musical training prior to hearing loss, listening habits, satisfaction with music listening, quality of music, enjoyment of musical styles, enjoyment of different instrumental timbres. This questionnaire was completed by preoperatively (N = 50) and at the 6-month interval (N = 48). The results provided by the applicant address certain aspects of the MBQ considered as the key aspects. For example, subjects reported an increase in musical enjoyment and an increase in the number of hours of music listening after receiving a Hybrid L24. Similarly, at the 6-month interval, 83.4% (40/48) of the subjects reported preferring to listen to music in the Combined Mode or Bimodal Mode. Together, the results from MBQ do not reveal any evidence that music enjoyment is compromised when music listening was achieved when bilateral (electric and acoustic) inputs were available.

Together, the patient-reported outcomes as derived from the SSQ, DUQ, and MBQ indicate overall improvement or no change in perceived benefits and satisfaction with the Hybrid L24 post-operatively than pre-operatively. There are, however, some inherent limitations with the SSQ, DUQ, and MBQ findings in the context of this study. First, not all of these instruments were psychometrically validated for the intended patient population for the Nucleus Hybrid L24. Second, because the present study design lacks a control group and is not blinded, interpretation of the questionnaire results may be biased by the placebo effect.

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

A. Panel Meeting Recommendation

At an advisory meeting held on November 8, 2013 the Ear, Nose, and Throat Devices Panel . voted 14-0-0 (yes-no-abstain) that there is reasonable assurance that the device is safe, 14-0-0 that there is reasonable assurance that the device is effective, and 13-0-1 that the benefits of the device outweigh the risks in patients who meet the criteria specified in the proposed indication.

The 24-hour panel-meeting summary is available at the following link: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/EarNoseandThroatDevicesPanel/ucm373789.htm

B. FDA's Post-Panel Action

FDA accepts the Panel's recommendations. Given the available data and the Panel discussion concerning the indicated population, FDA subsequently recommended that the device be indicated for unilateral use at this time, and the applicant agreed.

Additional clarifications to the device labeling including the indications for use have also been made based on Panel discussion and the clinical study.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

Two co-primary and three secondary effectiveness endpoints were defined. For all endpoints, performance at six months post implantation was compared to pre-operative baseline. Performance was primarily measured unilaterally, i.e., using the Hybrid L24 alone (at 6 months) and compared to the preoperative, hearing aided performance in the ear-to-be-implanted (at preoperative baseline). The two co-primary effectiveness endpoints were defined as a mean improvement in CNC word and AzBio sentence-in-noise scores. Three secondary effectiveness endpoints were defined in terms of the proportion of subjects who performed similar to or better at 6 months versus baseline for the following metrics: CNC words, CNC phonemes, and AzBio sentences in noise.

Co-Primary Endpoint Results: The mean improvement in CNC words was 35.7% with 95% confidence intervals of (27.8%, 43.6%). The mean improvement in AzBio was 32.0% with 95% confidence intervals of (23.6%, 40.4%). These improvements were statistically significant (both *p*-values < .0001), and it was thus concluded that both co-primary endpoints were met.

Secondary Endpoint Results: More than 75% of the subjects performed similar to or better on each of the three specified measures: CNC words (96%), CNC phonemes (90%), and AzBio (88%). All secondary endpoints were met.

Other effectiveness measures and analyses

Everyday Listening (Bimodal and Combined) testing: Data were also collected bilaterally (i.e., including a hearing aid on the contralateral side at 6 months) and compared with the baseline bilaterally aided condition. For each of the three secondary endpoints, all of subjects' scores (100%) were similar to or better than their preoperative performance.

Effect of baseline characteristics on endpoints: Post hoc analysis was conducted to see which, if any, of the six baseline variables (age, gender, duration of hearing loss of any degree, duration of severe-to-profound high-frequency hearing loss, preoperative CNC word score, or preoperative low-frequency hearing sensitivity) affected outcome(s). Multivariate analyses revealed that two baseline characteristics (pre-operative low-frequency hearing thresholds and duration of hearing loss) were each negatively associated with both CNC words and AzBio. The inference from these results is that a better pre-operative low-frequency hearing threshold and/or a shorter duration of hearing loss may be associated with better effectiveness performance.

Effect of postoperative low-frequency residual hearing on effectiveness: Post hoc analyses were conducted to examine the effect of postoperative low-frequency hearing on effectiveness. The common finding from these analyses was that the more hearing that was preserved, the better the outcome. This occurred when residual hearing sensitivity, or alternatively, the amount of hearing loss, was treated as either a continuous or a discretized variable (due to stratification).

When hearing loss was treated as a continuous variable, there was a negative correlation between each of the co-primary endpoints and loss of residual low-frequency hearing, both in terms of the amount of the amount of low-frequency loss and the hearing sensitivity (i.e., hearing thresholds) at 6 months. That is, the more preserved low-frequency hearing at 6 months, the better the device effectiveness.

In terms of analysis by discretized levels of hearing loss, the applicant stratified postoperative low-frequency hearing sensitivity into two groups: Group 1 (thresholds better than 90 dB HL) or Group 2 (thresholds poorer than or equal to 90 dB HL). Of the 50 subjects, 33 (66%) were thus classified as Group 1 and 17 (34%) as Group 2. In terms of CNC word recognition scores, the mean of Group 1 was 47% (SD = 20%), which greatly exceeded the mean of Group 2: 14% (SD = 28%). This suggests that preservation of residual hearing is important for CNC word recognition. In addition, almost all Group 1 subjects improved in CNC word recognition performance, whereas, in Group 2, only about half of the subjects did. The mean AzBio score of Group 1 was 45% (SD = 24%) while for Group 2 was 7% (SD = 22%) suggesting that preservation of residual hearing is important for AzBio sentence recognition. In addition, almost all Group 1 subjects improved their AzBio test scores from baseline, whereas, in Group 2, only about a third of the subjects improved, while a third of subjects performed more poorly.

Benefit was defined post hoc by FDA as improvement on at least one co-primary endpoint test at 6 months versus baseline. For Group 1 subjects, all (100%) of the 33 subjects improved in at least one test. However, for Group 2 subjects, nearly half (8/17) did not improve in either test.

Analysis by study site: The consistency of the primary endpoints was examined across investigational sites by testing for an effect of site in an ANOVA model, based on 49 subjects who completed the 6-month speech recognition tests. The results indicated no evidence of site effects on the primary effectiveness endpoints.

Other Effectiveness Measures:

UW-CAMP Music Perception: The results from 46 subjects with available data at 6 months postactivation indicated no change in performance on each of the three subtests compared to baseline. Further analysis revealed that subjects who experienced profound/total loss of residual low-frequency hearing performed, on average, more poorly compared to baseline on two UW-CAMP subtests: pitch discrimination and melody identification.

B. Safety Conclusions

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

The primary safety objective was to report all surgical and/or device-related events, as the number and proportion of individuals experiencing an adverse event.

- Loss of residual low-frequency hearing was the most frequently observed anticipated unresolved adverse event. Profound/Total loss was observed in 22 of 50 subjects (44%).
- Tinnitus related issues, device related open shorts, and dizziness related issues were the most frequently observed resolved adverse events and occurring at a rate of 28, 22, and 18%, respectively, in the 50 enrolled and implanted subjects.
- Explantation and reimplantation with a standard cochlear implant occurred in 6/50 (12%) of subjects as of February 10, 2014.

Observed adverse events that were resolved were consistent with those seen with approved cochlear implant systems. It is yet to be determined over the long-term how many additional subjects who experience profound loss will be explanted and re-implanted with a traditional cochlear implant array. The post approval studies which are specified in the approval order are designed to assess the time course of hearing loss and explant/reimplant rate. Based on the results of these post approval studies, the labeling for the Hybrid L24 will be updated accordingly.

C. Benefit-Risk Conclusions

There are limited options for the indicated population as reflected in the poor CNC word recognition performance even with appropriately fit bilateral hearing aids. The clinical study results for the Hybrid L24 that, on average, the Hybrid L24 is expected to improve speech recognition (in terms of CNC words and AzBio sentences) for a majority of the indicated population.

However, the profound and possibly also total loss of low-frequency hearing that occurred in 22/50 (44%) of subjects is a known risk and renders the device usage to electrical (cochlear implant) stimulation only since the acoustic amplification is ineffective for these levels of hearing loss. For subjects who lost low-frequency residual hearing to the profound/total level(s), the device showed benefit for only about half (9 of 17) or 53% of these subjects. Furthermore, 6/50 subjects who lost residual low-frequency hearing chose to undergo explantation of the Hybrid L24 and be reimplanted with an approved standard cochlear implant. The long-term rate of explantation/reimplantation is being studied in a post-approval study.

The clinical study results highlight the importance of preserving residual hearing in the contralateral ear since all subjects performed similar to or better than baseline in the Everyday Listening conditions (which utilize acoustic hearing in the contralateral, non-implanted ear) versus the Hybrid (alone) condition. These results indicate the important role of contralateral acoustic hearing for device effectiveness and support the indication for unilateral use for the device at this time.

FDA has determined that the overall hearing benefits of the device outweigh this risk for this population who do not benefit from traditional hearing aids. Prospective patients should carefully discuss all benefits and risks of this new device with their physicians. In terms of fitting the device and patient counseling, clinicians should consider the duration of hearing loss for potential candidates since this is listed in both in the contraindications (device labeling) and in the exclusion criteria for the clinical study. This advisory is also supported by the exploratory analysis suggesting that a shorter duration of hearing loss and/or better pre-operative low-frequency hearing sensitivity may be associated with better effectiveness performance.

Given the benefit-risk profile for the device, the Indications for Use for the Hybrid L24 clearly lists the following restrictions: unilateral usage of the device and a sufficient trial of conventional hearing aids. The labeling also includes a sufficiently detailed and complete summary of the study finding for clinicians and provides counseling recommendations based on the clinical study results.

These recommendations were discussed during the November 8, 2013 panel meeting for the Hybrid L24 where the Panel voted 13-0-1 (yes, no, abstain) that the benefits of the Hybrid L24 do outweigh the risks for use in patients who meet the criteria specified in the proposed indication.

D. Overall Conclusions

The data in this application support a reasonable assurance of safety and effectiveness of this device when used in accordance with the proposed indications for use. The provided preclinical testing for the device was acceptable. Based on the clinical study results, it is reasonable to expect clinical benefits with use of the Nucleus Hybrid L24 Cochlear Implant System in terms of improvement in speech understanding in quiet and noise since the average performance of the study population showed statistically significant improvements in these two co-primary endpoint measures. While improvement was observed on the average, for individuals who lost residual low-frequency hearing to the profound level, the device was less likely to provide benefit compared to when more hearing was preserved. Music perception performance using the Hybrid L24 did not, on average, change compared to hearing-aided baseline, although individual performance appeared to again relate to the amount of preserved residual hearing. Six study subjects opted to be explanted and reimplanted with a traditional cochlear implant due to reasons that include hearing loss and dissatisfaction. The risks associated with the device, including residual low-frequency hearing loss and the risk of explantation/reimplantation should therefore be carefully

considered by potential candidates and their hearing health-care providers. However, FDA believes that the available data demonstrate that the benefits outweigh these risks in the pivotal study patient population, particularly since the device provided speech-understanding benefit for most subjects, including even the majority of individuals who lost residual hearing to the profound levels.

XIV. CDRH DECISION

CDRH issued an approval order on March 20, 2014. The final conditions of approval cited in the approval order are described below.

***Extended Follow-up Study**:* This study is an extended follow-up of the subjects who were enrolled in the pivotal study to assess long-term device performance. The study will be conducted as a prospective, non-controlled, non-randomized, multicenter study at the 10 sites. All 39 available subjects who were enrolled in the pivotal study will be invited to participate in the extended follow-up. Study subjects will be followed for 5 years post-implantation of the device. The primary safety endpoint is the comparison of the type and frequency of adverse events and serious adverse events observed during the duration of the study compared to the pivotal study. 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 in noise as evaluated with the AzBio test (+5dB SNR). The change in the perceived hearing benefits, patient satisfaction with the device use and quality of life will be assessed by employing patient reported questionnaires. Follow-up will occur at 36, 48 and 60 months post-implantation. Every explanted device will be tested to determine the reason for device failure, and device explantations will be reported as serious adverse events.

***New Enrollment Study**:* The purpose of this study is to provide longer-term data on the safety and effectiveness of the Nucleus Hybrid L24 Cochlear Implant System under general conditions of use in the postmarket environment. This study will be conducted as a prospective, non-controlled, non-randomized study in 25 clinical sites. A total of 100 subjects newly treated will be enrolled. Study subjects will be followed for 5 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 duration of the study compared to the pivotal study. 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 in noise as evaluated with the AzBio test (+5dB SNR). The change in the perceived hearing benefits, patient satisfaction with the device use and quality of life will be assessed by employing patient reported questionnaires. Follow-up will occur at 3, 6, 12, 24, 36, 48 and 60 months post-implantation. Every explanted device will be tested to determine the reason for device failure, and device explantations will be reported as serious adverse events.

The applicant's manufacturing facility has 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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