SUMMARY OF SAFETY AND EFFECTIVENESS

I. GENERAL INFORMATION

Device Generic Name:	Auditory Brainstem Implant
Device Trade Name:	Nucleus® 24 Auditory Brainstem Implant System
Applicant's Name and Address:	Cochlear Corporation 61 Inverness Drive East Suite 200 Englewood, CO 80112
Premarket Approval (PMA) Application Number:	P000015
Date of Panel Meeting:	July 21, 2000
Date of Notice of Approval to Applicant:	October 20, 2000
Expedited Review:	Expedited processing was authorized on July 14, 2000 since no other alternative exists following tumor removal and severing the auditory nerve to treat the intended patient population.

II. INDICATIONS FOR USE

The Nucleus 24 ABI is intended to restore useful hearing via electrical stimulation of the cochlear nucleus. This device is indicated for individuals 12 years of age or older, who have been diagnosed with Neurofibromatosis Type 2 (NF2). Implantation may occur during first- or second-side tumor removal or in patients with previously removed acoustic tumors bilaterally. Because the surgical tumor excision and electrode placement eliminates residual hearing, preoperative audiological criteria are not relevant. Prospective implant recipients and their families should have appropriate expectations, regarding the potential benefits of an auditory brainstem implant, and should be highly motivated to participate in the rehabilitation process.

III. CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

Contraindications: None known.

Warnings and Precautions: See package insert.

IV. DEVICE DESCRIPTION

The Nucleus 24 ABI is an implanted device that is used in conjunction with a body-worn (SPrint™) external speech processor. An ear-level microphone converts sound into an electrical code that is delivered to electrodes placed on the brainstem, that in turn stimulate the neurons of the cochlear nucleus. Coded information from the SPrint speech processor is delivered across the skin via electromagnetic induction to the implanted receiver/stimulator that is surgically placed in the bone behind the ear. The SPrint processor is programmed with the SPEAK speech processing strategy and delivers information to each of the 21 electrodes placed on the brainstem, depending on the information present in the incoming sound, at levels that are appropriate for the individual recipient.

The Nucleus 24 ABI System consists of the ABI24M implant, the body-worn SPrint speech processor, and a Clinical Programming System. The Clinical Programming System consists of Windows-based programming software and either a portable or "PC"-based hardware platform.

Nucleus 24 System Components

ABI24M Implant: The ABI24M implant consists of an electronics package (receiver/stimulator) hermetically housed in titanium, a platinum receiver coil (antenna) encased in silicone elastomer, a 21-electrode brainstem array, and two ground electrodes. The receiver stimulator contains a hybrid module, with a custom-designed Large Scale Integration (LSI) High Reliability Integrated Circuit and a reduced number of passive components. The receiver coil is preformed at an angle designed to conform to the curvature of the skull.

The electrode array consists of 21 active platinum disk electrodes, mounted on a 3 x 8.5 mm silicone carrier backed with PET mesh. Each of the 21 electrodes is .7 mm (+/- 0.1 mm) in diameter. The electrode lead is coiled and highly flexible and exits the receiver/stimulator from its medial surface to improve robustness.

Two capacitively coupled ground electrodes (a plate electrode on the lateral surface of the receiver/stimulator, and a ball electrode placed beneath the temporalis muscle) allow multiple modes of stimulation (e.g., monopolar, bipolar, and common ground) to be programmed by the clinician. The two ground electrodes provide redundancy, additional programming flexibility, as well as the

basis for Neural Response Telemetry (NRT). NRT is a unique component of a comprehensive bi-directional telemetry system that provides a detailed assessment of the implant's status, and measures the auditory system's physiological responsiveness to stimulation from the implant.

The ABI24M has the ability to deliver stimulus pulses ranging from 10 μA to 1750 μA (in logarithmic steps) in amplitude, with pulse durations as low as 25 μsec, at stimulation rates up to 14,400 Hz. To ensure safety, the ABI24M delivers carefully balanced biphasic current pulses, shorts all electrodes to a common point between stimulus pulses, and capacitively couples the two ground electrodes.

SPrint Speech Processor: The SPrint is a fully programmable body-worn speech processor implementing Digital Signal Processing technology that allows for a wide range of strategies to be programmed. Recipients may select from up to four independent speech processor programs. The SPrint is controlled by seven buttons that may be programmed by the audiologist to include separate volume and sensitivity controls, a series of private or audible alarms, and/or locks. The functional status of the SPrint is indicated by a custom liquid crystal display (LCD) on the front panel (e.g., selected program, sensitivity/volume settings, battery status, and alarm functions). A number of accessories, such as a TV/HiFi adaptor and personal audio cable, allow direct connection of external sound sources.

The SPrint performs a series of safety-related functions, such as error detection within signal processing programs, utilization data, and monitoring of battery life. A single-battery or double-battery module may power the speech processor.

V. ALTERNATIVE PRACTICES AND PROCEDURES

Alternative treatments for NF2 patients with total bilateral deafness include tactile devices, the use of manual communication (i.e., sign language), and/or additional lipreading practice and training. Tactile devices are worn externally and convert sound waves into mechanical vibration or electrical current that can be detected on the skin by the wearer.

VI. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

CLINICAL CONSIDERATIONS

In order to place the electrode array on the surface of the cochlear nucleus, the surgeon must be able to visualize specific anatomical landmarks. Because many NF2 patients have large tumors that compress the brainstem and distort the underlying anatomy, it may be difficult or impossible for the surgeon to correctly place the array. For this reason, patients with large, longstanding tumors may not benefit from the ABI device, postoperatively. In

this series of patients, 16 of the 90 recipients (17.8%) were unable to use the ABI system, postimplantation, due to misplacement or migration of the electrode array.

Patients who receive the ABI at the time that their first tumor is removed, and who have useable hearing in the contralateral ear, are unlikely to use the ABI device on a regular basis. Most often, these recipients assume full-time use of the device, following the surgical removal of their second-side tumor.

ADVERSE EFFECTS

Prospective implant recipients should be told of the following possible effects of receiving an implant.

- Individuals are exposed to the normal risks associated with surgery and general anesthesia. In addition, this procedure may result in infection or bleeding, numbness or stiffness around the ear, injury to or stimulation of the facial nerve, taste disturbance, dizziness, increased tinnitus, neck pain and leakage of cerebrospinal fluid. Leakage of cerebrospinal fluid may result in meningitis.

- Risks include those generally associated with a craniotomy operation, in addition to those associated with the implantation of the ABI electrode and receiver/stimulator. Potential recipients should understand that circumstances encountered during surgery may preclude placement of the ABI, and also that the tumor removal surgery results in a total loss of hearing on the operated side.

- The ABI results in a palpable lump under the skin behind the ear. The presence of a foreign body may cause irritation, inflammation or breakdown of the skin and in some cases, extrusion of the device.

- Postoperatively, the electrode array may migrate partially or completely away from the cochlear nucleus, resulting in decreased hearing, a complete loss of sound perception, and/or increased nonauditory sensations. In addition, if the electrode array is misplaced at the time of surgery, the recipient will not receive functional benefit from the device. Such complications may require additional medical treatment, surgery, and/or removal of the ABI.

- Electrical stimulation may result in increased tinnitus, facial nerve stimulation, dizziness or pain. In addition, electrical currents generated by the ABI may spread and stimulate other adjacent brainstem structures. This may produce a variety of nonauditory sensations or movements, such as a tickling sensation in the back of the throat, visual field disturbances, and sensations and/or movements in a limb. In rare cases, electrical

stimulation may cause other neurological sequelae that may be severe.

- The long-term effects of electrode insertion and chronic electrical stimulation are unknown. Such effects may preclude replacement of the electrode array, or may lead to eventual deterioration of nerve cells in the central auditory nervous system.

- Failure of component parts (both external and internal) could result in the perception of uncomfortably loud sounds, the complete absence of sound, or in unwanted nonauditory sensations. Failure of various parts of the implanted device could require its removal and/or replacement, or could result in a reduced number of useable electrodes.

VII. MARKETING HISTORY

The first Nucleus 22 and 24 ABI surgeries occurred in the U.S. in 1993 and 2000, respectively, as part of the FDA-monitored Clinical Trial (IDE G930077). The Nucleus 24 Auditory Brainstem Implant currently may be sold in over 40 countries. Cochlear was authorized to affix the CE Mark to the Nucleus 22 ABI system in August 1998 (Certificate No. II, 9610582 02), and to the Nucleus 24 ABI in April, 1999 (Certificate No. II, 9910586 01). As of March 2000, a total of 140 individuals were implanted with a Nucleus ABI in the United States, Europe, Australia, Japan, and Argentina. Neither the Nucleus 22 nor the Nucleus 24 ABI has been withdrawn from any country for any safety or efficacy reason. The newer Nucleus 24 ABI is now distributed in place of the Nucleus 22 ABI, which is no longer manufactured. Cochlear Corporation intends to service all patients with the Nucleus 22 ABI.

VIII. SUMMARY OF STUDIES

A. Nonclinical Laboratory Studies

The Nucleus 24 ABI System is identical – apart from the electrode array design - to the Nucleus 24 Cochlear Implant System. Thus most of the nonclinical studies that were undertaken to evaluate the safety and fitness for use of the Nucleus 24 Cochlear Implant System are relevant to the Nucleus 24 ABI System. Generally the studies performed have closely followed the existent applicable regulatory and/or industry standard requirements. However most of these studies were not strictly compliant to the Good Laboratory Practice for Nonclinical Laboratory Studies Requirements (21 CFR 58). The sponsor believes that these studies were conducted in such a manner as to give assurance to the quality and integrity of their data.

The results of these activities are summarized below and demonstrate, with a reasonable degree of assurance, that the Nucleus 24 ABI System is safe and effective for its intended use.

1. Electrode Design

The characteristics and limitations of the translabyrinthine approach have imposed geometry (shape and size), flexibility and stability requirements in the case of the surface electrode carrier, conditions that are reflected in the present design of the ABI24M electrode array.

The design of the surface electrode array is optimized for maximal adhesion to ensure minimal or no migration in or out of the lateral recess [14]. Additionally, the T-shaped PET mesh can be cut to an optimum size/shape, to ensure additional adhesion to the brainstem and that the electrode carrier does not move with brain pulsations. These design features function to minimize the likelihood of carrier migration, after the placement of the array on the brainstem.

Nonclinical chronic in-vivo laboratory studies, [8], have confirmed the stability of the implanted surface electrode array which was fixed on the cochlear nucleus using a PET mesh, which was invaded by fibrous tissue growth in a relatively short time after the surgery.

2. Safety of ABI24M Stimulation

The ABI24M stimulator is capable of both bipolar and monopolar stimulation. For both stimulation modes, the stimulation regime is identical to that used in the previously PMA approved CI24M and CI22M cochlear implants. The safety of electrical stimulation of the cochlea, as implemented by the CI24M device, has been demonstrated via field use by patients from all age categories, as well as in nonclinical chronic and acute studies. Comparatively, the quantity of experimental data pertaining to the electrical stimulation of the cortex is small. A series of nonclinical and clinical studies, using the ABI24M device or similar prostheses, tend to confirm that similar safe limits are valid for both electrical stimulation of the cochlear and the cortex.

Both acute and chronic nonclinical studies, such as [3], [5], [6], demonstrate that long-term electrical stimulation safety limits are similar for both cochlear and brainstem stimulation. Histological results in acute animal studies have failed to indicate any significant effects at the surface or in the volume of the cochlear nucleus, due to electrical stimulation, under the selected test conditions in each of these studies. The experiments generally concluded that acute or chronic stimulation is safe for neuronal excitation of the cochlear nucleus in the selected animal models, providing that the main stimulation parameters, such as charge per phase and/or charge density per phase, are kept below certain limiting values. Significantly, McCreery et al., [7], obtained data relevant to safe/unsafe stimulation levels for surface stimulation of the cortex, that allowed the study (and development of a model by Shannon RV [15]) of the non-linear relationship between the charge per phase, charge density per phase, and the geometrical characteristics of the stimulating surface electrode.

These results (and the model developed in [15]) can be used to derive a *highly conservative* estimate for the limits of charge and charge density per phase that can be safely used with the ABI24M system, considering that:

a) The data obtained by McCreery et al., were obtained using AF (Anodic First) pulses; whereas, CF (Cathodic First) pulses are provided by the ABI24M system. The use of CF pulses significantly extends the safe limits imposed by electrode-tissue interface effects [17].

b) It has been shown that stimulation duty cycle has a significant influence on both the threshold for injury and the severity of injury. For example a 50% stimulation duty cycle, which is characteristic of present speech processing strategies used under normal environmental conditions, significantly limits the severity and potential for injury (and may completely abolish it), at values of charge and charge density per phase approximating those at the threshold for damage (see [15] for results using a duty cycle of 100%).

Results of a more recent animal study [16], concerning surface electrical stimulation of the primate cochlear nucleus (Macaca fascicularis), tend to strengthen the above conclusions, and are in agreement with the values derived in [15], under the conditions of increased rate (500Hz) and decreased (33%) duty cycle.

Additionally, the proximity of the cochlear nucleus to the other cranial nerves suggests that care should be taken to limit the likelihood of adjacent nerve or cerebellar stimulation. Several pilot studies have shown that the electrical stimulation of the brainstem at the ABI24M electrode location may result in the stimulation of cranial nerves and other brainstem structures, and that this unwanted stimulation is a function of stimulation level, pulse width, and frequency [14]. In addition, nonauditory thresholds were significantly higher than auditory threshold levels (i.e., a one order of magnitude difference at 300Hz, that decreased as a function of increasing stimulus frequency). There is, however, an independent chance of unusual current spread, misplacement of the electrode array, or incomplete insertion in the lateral recess that also may result in nonauditory stimulation.

3. Measurement of DC Levels

A multitude of factors contribute to the presence and magnitude of residual direct current levels, and there is an intricate relationship between the level of direct current and the likelihood of risk to tissue. Direct current in the several microamperes range has been associated with neural tissue damage. The ABI24M delivers a biphasic stimulus waveform, which is charge balanced. There may be some asymmetric processes at the electrodes that may result in a non-zero net direct current level. To minimize the level of any potential direct current

to values well below the known safe value, the ABI24M uses capacitively coupled monopolar electrodes. Furthermore, the receiver/stimulator uses a patented charge-recovery system, that has been proven effective in minimizing the level of direct current to levels below those associated with tissue damage, both at low and high stimulation rates.

Similar conclusions were reached in a more recent *in vivo* study [11], where levels of direct current were measured as a function of stimulation rate. Although the experiment was conducted using the CI24M cochlear implant, the results can be applied to the ABI24M, as the two devices share the same receiver/stimulator. The measurements were taken using a continuous stimulation pattern (i.e., 100% duty cycle) and, thus, were more severe than a worse-case listening environment. The results of this study indicated that average magnitudes of direct current delivered to the cochlea by the CI24M device, at maximum stimulation levels and using a total stimulation rate of 2000 Hz, were below 20 nA for monopolar stimulation and 30nA for bipolar stimulation. Both of these values were well below the known biologically safe value for long-term direct current delivery to the auditory nerve or cochlea. Finally, this study also confirmed that there was no significant difference between levels of direct current in monopolar and bipolar stimulation modes, under normal functional conditions.

4. Electromagnetic Interference (EMI) and Electrical Safety Tests

Susceptibility to electromagnetic fields, radiated electromagnetic fields, and electrical safety tests (including susceptibility to electrostatic discharge) were conducted on the CI24M receiver/stimulator, which is identical to ABI24M. The tests were in accordance with the requirements of applicable standards, and the systems tested were compliant with all applicable regulatory requirements (such as those defined in the AIMD standard, IEC 801-2 (Electrostatic Discharge Requirements), and IEC1C801-3 (Radiated Fields Requirements), IEC601-1 (Medical Equipment, General Safety Requirements) with Amendments 1&2, etc.

5. Mechanical and Environmental Tests

As the ABI24M device uses the same stimulator and coil assembly as the CI24M cochlear implant, environmental tests performed on CI24M may be applied with confidence to the ABI24M. The only difference between the two devices (i.e., the electrode array) had no possible impact on the environmental test results. However, as summarized below, the ABI's unique electrode was subjected to additional dynamic fatigue testing.

Linear and Angular Fatigue Test of the Electrode Array: A total of 12 units were exercised through +/- 30^0 angular (four units) and +/-10% of electrode length (eight units) at about 2 cycles per second, in a number of different test planes. The samples passed 2.5 million cycles, while maintaining continuity and showing no visible signs of damage.

Electrode Flex Test: The main purpose of this test was to verify that the connection of the lead wire to the disc electrode would not sustain damage, while withstanding flexing similar to that which could occur during manufacture and implantation. Two arrays were used, given that there are 42 connections of this type in two electrode pads. The test sample was placed between the two pins in a test jig. Using a finger flex, the electrode was flexed around the pins for a total of 10 times in each direction. The sample was inspected under magnification for signs of any damage to the electrode. The electrical continuity of the electrode also was inspected and all acceptance criteria were fully met.

The series of tests that apply to the ABI24M device, and were conducted, using the CI24M receiver/stimulator is summarized below. They have been devised to assess the implant's ability to withstand extreme environmental conditions, which may potentially be experienced during manufacture, shipping and typical use. Six types of tests were employed, as follows.

Dynamic Fatigue Testing

These tests included a large number of cycles, implemented at low stress levels.

Mechanical Test to Load / Deformation of the Receiver Coil: The samples passed 2.5 million cycles, while maintaining continuity and showing no visible signs of damage.

Severe Stress Testing

This series of tests were characterized by a low number of cycles, implemented at high stress levels. The tests were designed to determine the effects of extreme stress on the CI24M receiver/stimulator, that potentially could occur during the manufacturing or handling process, implant surgery, or in the event of a severe mechanical trauma to the patient. A variable number of samples were tested during each of the tests. Each time, the acceptance criteria were met and the tests successfully passed.

Severe Stretch and Twist of the Electrode Lead: The electrode lead was bent at an angle of 90^0 to the receiver/stimulator body and then stretched to 110% of its normal length. Maintaining the angular orientation and stretching force, the lead was rotated 360^0 clockwise in a plane perpendicular to the receiver/stimulator body and then 360^0 counter-clockwise over 10 cycles. The sample showed no electrical failure or significant damage.

Severe Bending Test: The receiver coil was bent to an angle of 180^0 relative to its original position and then reversed for 10 cycles. The sample showed no evidence of damage.

Severe Twist Test: The receiver coil was rotated clockwise, to an angle of 90° around the longitudinal axis of the receiver/stimulator, then counter-clockwise to 180° and, finally, another 90° clockwise (to return to the normal position). This sequence was repeated 10 times and the sample showed no evidence of mechanical deformation, electrical failure or visual defect.

Severe Electrode Lead Shear Test: The electrode lead was clamped at a 90° 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) into the lead. There were no failures resulted in the three test specimens.

Destructive Testing

To determine the limits of the design, the following tests were conducted using a single cycle, implemented at a very high stress level. A variable number of samples were tested during each of the procedures.

Tensile Strength of the Electrode and the Electrode/Lead Wire Configuration: The tensile strength of the electrode structure was not significantly less than that of the annealed lead wire.

Activity Testing

These tests were designed to determine the ability of the receiver/stimulator to withstand severe conditions that could occur during various sporting activities. A variable number of samples were tested during each of the procedures. Each time, the acceptance criteria were met and the tests successfully passed.

High-pressure Test: Sample receiver/stimulators were subjected to 5 atm pressure for 15 minutes. There was no physical or electrical damage to the device that could degrade functionality, performance, or physical appearance.

Severe Impact Test: This test assessed the potential effects on the receiver/stimulator of an impact of a 100g projectile, traveling at a velocity of 64.5 Km/hr. The receiver/stimulator withstood this impact without damage.

Receiver/stimulator Crush Test: This test evaluated the maximum crush pressure that the receiver/stimulator was able to withstand without damage. A pressure of 1.4 MPa was applied normal to the implant, situated on a bed simulating bone and soft tissue. The receiver/stimulator withstood this test without any electrical failure.

General Testing

These tests are designed to evaluate the effects of the environment of the human body, or the application of various medical technologies in the vicinity of the implanted device. Each time the acceptance criteria were met and the tests successfully passed.

Fatigue Under Repeated Headset Manipulation: An angular deflection of +/- 30° was applied to the receiver coil, resulting in a linear deflection of approximately 4 cm. A layer of silicone was stretched and fastened across the aperture side of the implant, simulating tissue overlying the device. Angular deflection was tested over .75 million cycles, at approximately 2 cycles per second. No visible signs of damage were observed.

Environmental Testing

These tests are designed to evaluate the implant's ability to withstand extreme environmental conditions, that potentially could occur during manufacture, shipping and typical use. Ten samples were used in each of the environmental tests. Following testing, each specimen was evaluated and determined to be hermetic.

Vibration Test (IEC 68-2-47): The test sample was subjected to random vibration at a frequency bandwidth of 5 to 150 Hz, at an acceleration spectral density of 0.1 g^2/Hz for 30 minutes, across three orthogonal planes. No physical or electrical damage was observed.

Thermal Cycling Test (AS 1099.2., Test Nb): Samples were subjected to five alternating thermal cycles from 50° (+3/-0°) Celsius to -40° (+0/-5°) Celsius, with 30 minutes at each temperature and 15 minutes in between. No physical or electrical damage occurred.

Pressure Cycling Testing: Samples were subjected to 5 pressure cycles, ranging from 2 atm to 0.1 atm. No physical or electrical damage effecting functionality, performance, or physical appearance was noted.

Shock Acceleration Testing (AS 1099, Test Ea): Samples were subjected to 18 shocks of half sine pulses at 500 g for a duration of 1ms. The 18 shocks were comprised of three shocks in each direction, along three mutually perpendicular directions. No physical or electrical damage was noted.

Dry Heat Testing (AS 1099, Test Bd): Samples were exposed to temperatures ranging from to 100^{0}C for two hours to 50^{0}C for 12 hours, with relative humidity maintained at 50% or below. Following the test, there was no physical or electrical damage.

Cold Temperature Testing (AS 1099, Test Aa): Samples were exposed to temperatures ranging from -25^{0}C for 4 hours to 5^{0}C for 12 hours, with no resulting physical or electrical damage.

ETOH Sterilization Test: The manufacturer successfully validated The ABI24M implant for ethylene oxide.

6. Failure Modes, Effects and Criticality Analysis and Hazard Analysis

Given the equivalence of the ABI24M and CI24M receiver/stimulators, quantitative and qualitative analyses performed to identify and estimate the likelihood of potential safety hazards associated with the use of the Nucleus CI24M Cochlear Implant also are valid for the ABI24M device. No failure that could lead to a life-threatening situation was identified. Based on the severity of the potential failures and on their estimated probability of occurrence, most of the identified failure modes were classified as Risk Class III, ('Low Risk') or Class IV ('Very Low Risk'). There were, however, some Class II risks identified, that were attributed to intraoperative and postoperative procedures, as opposed to any device characteristic.

The theoretical failure rate, derived from the electrical and mechanical reliability characteristics of the components, interconnections and materials used in the ABI24M was estimated to be approximately four failures in 100 implants per 10 years (with 90% probability). The observed failure rate for the ABI24M is presently zero.

7. Biocompatibility

The design of ABI24M electrode array incorporates 21 disk electrodes made of 99.99% platinum. The biocompatibility of Pt electrodes has been repeatedly verified in nonclinical chronic *in-vivo* studies such as [2] and [8].

The carrier is made out of biocompatible silicon-elastomer and backed up by a compatible PET mesh. The safety of the surface carrier relative to potential irritative effects on the adjacent and subjacent brainstem tissue has been analyzed in studies such as [8], and compared to a penetrating-electrode approach in [4]. The findings of the above two studies were verified during postmortem examinations and also during removal of an electrode array from a human recipient [12]. These studies have generally found no histopathological changes at the brainstem following chronic ABI implantation, in both animals and humans, due to the presence of the ABI24M surface electrode carrier.

A more recent study [8] of primates, suggested that there were no significant surface adverse reactions at subjacent brainstem structures, due to the presence of an electrically inactive ABI24M surface electrode array. The absence of injury at the cochlear nucleus level after explanation of the array also supported the

feasibility of re-implantation surgery. Similar results were obtained in an acute animal study, using an electrically stimulated electrode carrier, similar to the one used in the ABI24M. The study concluded that there were no significant histological differences between the electrically stimulated surface electrodes and the cochlear nucleus control site in both animal species, either at the surface or within the cochlear nucleus volume. Similar results were obtained in [6].

The ABI24M uses the same materials, which have been demonstrated as biocompatible, in the commercially released CI24M and CI22M cochlear implants, surgically implanted in more than 26,000 patients worldwide.

The biocompatibility of the following "tissue-contacting" materials was evaluated in a series of *in-vivo* and *in-vitro* studies using the equivalent CI24M device.

Dow Corning Silicone Rubber Medical Adhesive, Type A
Dow Corning Silicone Rubber tubing 602
Dow Corning Silicone Rubber MDX-4-4515
Dow Corning Silicone Rubber MDX-4-4210
Platinum Band - 99.9% Pure

Cytotoxicity (Dow Corning Silicone Rubber): The material was evaluated for cytopathic effect by placing the material in direct contact with a confluent monolayer of human embryonic cells. After an incubation period of 24 hours, the cytopathic effect was evaluated microscopically and compared with a positive and negative control. The material produced no cytopathic effect.

Systemic Toxicity (Dow Corning Silicone Rubber): Test material extracts from saline and cottonseed oil were injected into groups of mice (each group consisting of five mice). The mice were observed for systemic toxicity for up to 72 hours. There were no signs of toxicity.

Transcutaneous Irritation (Dow Corning Silicone Rubber): Test material extracts from saline and cottonseed oil were injected into rabbit skin and observed for local irritative effects for up to 72 hours. There was no evidence of significant irritation or toxicity.

Muscle Implantation Test (Dow Corning Silicone Rubber): A muscle implantation test was conducted in rabbits to evaluate the reaction of muscle tissue over a ninety-day period. No significant adverse effects were noted for both gross and histological examination.

99.9% Pure Platinum Band: Extensive documentation, demonstrating the acceptability of platinum as an electrode material for neurostimulation, is available in the literature. Platinum has been shown to be biocompatible with neural tissue by numerous investigators and the electrode material of choice in a variety of neuroprosthetic applications.

Test of Assembled Units: Five assembled Nucleus cochlear implants were implanted intramuscularly in cats for a period of approximately four weeks. On removal of the units, tissue biopsies were taken from tissue adjacent to the units and bacterial swabs of the package were collected. Tissue reaction to these materials was then evaluated histologically and no adverse reactions were apparent.

B. Clinical Studies

1. Study Objective

The study's objective was to validate the clinical function of the Nucleus ABI, programmed to implement the SPEAK speech-coding strategy, in a representative sample of subjects.

The clinical data in this PMA is from the clinical trial that was conducted on the Nucleus 22 ABI System. The PMA approval is for an updated version, the Nucleus 24 ABI System. The main difference is that the Nucleus 24 ABI utilizes a 21 electrode array, whereas the Nucleus 22 ABI uses an 8 electrode array. The Nucleus 24 ABI System is based upon the Nucleus 24 Cochlear Implant System (P970051) i.e. the speech processor, speech coding strategy, and simulator receiver are identical. The 21 electrode array (ABI) has been implanted in Europe utilizing the Nucleus 22 speech processor, speech coding strategy, and simulator receiver. Therefore, clinical data reported in the PMA and prior approval of the Nucleus 22 Cochlear Implant System support approval of the Nucleus 24 ABI System.

2 Subject Inclusion and Exclusion Criteria

Inclusion Criteria:

(i) Diagnosis of Neurofibromatosis Type 2; (ii) Twelve years of age or older; (iii) English as a primary language; (iv) Willingness to comply with all investigational requirements.

Previous single-channel ABI recipients were selected for this investigation if the existing, single-channel device was no longer functional.

Exclusion Criteria:

(i) Medical or psychological contraindications to surgery; (ii) unrealistic expectations regarding possible device-related benefits, risks and limitations.

3. Study Population Demographics

A total of 92 investigational subjects were implanted with the Nucleus 22 ABI and data from 90 of these subjects were submitted supporting device safety. Two of the 92 implanted subjects died of causes unrelated to the ABI, prior to device activation. Sixty subjects, with a minimum of 3 to 6 months experience with the device were submitted supporting device effectiveness.

The investigational sample supporting device effectiveness consisted of 41 females (68.3%) and 19 males (31.7%). Subjects ranged in age from 12 years to 67 years, with a mean age of 33.0 years. Twenty of these subjects (33.3%) were implanted during surgery to remove the first-side tumor, and forty subjects (66.7%) were implanted during second-side tumor removal surgery.

The investigational sample supporting device safety consisted of 56 females (62.2%) and 34 males (37.8%) and was in all respects very similar to the sample supporting device effectiveness. The mean age at implantation for the safety subjects was 33.4 years, with individual subjects ranging in age from 12 to 67 years. Thirty-three percent of these subjects (30/90) were implanted during their first-side tumor removal surgery. The remaining 67% (60/90) were implanted at the time of second-side tumor removal.

4. Summary of Safety Data

Ninety qualified subjects were implanted with the investigational ABI device at ten investigational sites. This series of adult and adolescent ABI recipients included the 60 subjects who were studied for device effectiveness, as well as 30 additional subjects who had yet to reach or complete their 3 to 6 month evaluation intervals. Of the 90 subjects studied for safety, 26 experienced a total of 28 medical or device-related complications. Twenty-two of the 28 complications were medical/surgical in nature and the remaining six were device related. Twenty-six of the 28 complications resolved without surgical or extensive medical intervention.

Medical/Surgical Complications

Sixteen of the 90 ABI recipients were not able to perceive sound with the ABI, postoperatively. This was either due to migration of the electrode array during the immediate postoperative period (9 patients), or to misplacement of the electrode array at the time of surgery (7 patients). Two additional patients experienced postoperative flap complications and, in both cases, surgical explantation of the ABI was required. Four patients experienced minor complications that resolved with noninvasive medical treatment (1 patient), reprogramming of the speech processor (2 patients), or spontaneously without intervention (1 patient). The first of these four patients experienced a build-up of fluid beneath the skin flap, the second reported dizziness, blurred vision and tinnitus during the perioperative period, the third reported lightheadedness and

dizziness during periods of ABI use, and the fourth patient experienced headaches when using the device.

Device-related Complications

No device failures or other serious device malfunctions occurred during this study. Two patients experienced a mild skin reaction to the ABI's retainer disk. One case was resolved by temporarily reducing the patient's daily use time and the second by providing the patient with an alternative method of adhesion. During the study period, two patients reported transient changes in the ABI's sound quality. These resolved over time in one case, and with device reprogramming in the second. Device reprogramming resolved one additional patient's report of pain, caused by activation of two specific electrode channels. A final patient reported hearing a transient popping sound that, subsequently, resolved without treatment.

5. Summary of Effectiveness Data

Device effectiveness was investigated using a single-subject, repeated-measures research design, with subjects acting as their own controls. Postoperatively, performance was assessed in 60 recipients of the Nucleus 22 ABI system, following 3 to 6 months of device use. Effectiveness of the ABI, programmed to implement the SPEAK speech processing strategy, was measured using a standard battery of recorded audiological tests, including measures of environmental sound identification, closed- and open-set speech perception, and lipreading enhancement. The environmental sounds and speech perception tests were administered to subjects in quiet, at 70 dB SPL. As a final measure of effectiveness, 44 of the 60 (73%) subjects completed and returned postoperative questionnaires, regarding device-related benefits.

6. Evaluation Measures

A variety of auditory tests were selected to assess device effectiveness, postoperatively, including measures of environmental sound identification, closed- and open-set speech perception, and lipreading enhancement. All tests were recorded, were administered in sound field, and were presented in quiet at 70 dB SPL. In addition to these standard audiological measures, subjects also completed postoperative questionnaires. The questionnaires were designed by the sponsor to assess device use, satisfaction, and each subject's ability to hear and understand with the ABI in different listening situations.

Environmental Sound Recognition: The Sound Effects Recognition Test (SERT) was used to measure each subject's ability to identify common environmental sounds, using sound from the ABI. The SERT consists of three sets of ten

common environmental sounds, presented in a four-alternative forced-choice paradigm.

Speech Pattern (Prosody) Identification: The Monosyllable/Trochee/Spondee (MTS) Test was administered in closed-set format, and scored as a measure of pattern perception. Twenty-four one- and two- syllable words were presented to each subject, and the individual's responses were scored according to the number of items correctly identified by their underlying stress pattern (i.e., monosyllable vs. trochee vs. spondee).

Closed-set Word Identification: Two test measures were used to evaluate closed-set word identification skills: the Northwestern University Children's Perception of Speech (NU-CHIPS) Test, and the Monosyllable/Trochee/Spondee (MTS) Word Test. The NU-CHIPS test was developed for use with hearing-impaired children, and was adapted for use with adult ABI recipients, by incorporating a written response format. This moderately difficult test consists of four lists of 50 monosyllabic words, presented in a four-alternative forced-choice paradigm. Compared to the NUCHIPS, the Monosyllable/Trochee/Spondee (MTS) Word Test is an easier test of closed-set word identification. The MTS test consists of 12 one- and two-syllable words, each of which was presented twice in a randomized fashion, for a total of 24 items.

Open-set Sentence Recognition: Open-set sentence recognition was assessed using Central Institute for the Deaf (CID) Sentences of Everyday Speech. Each of the 10 CID sentence lists consists of 50 key words and was scored according to the number of key words correctly identified.

Lipreading Enhancement: Three tests were selected as measures of lipreading enhancement: the Iowa Medial Vowel Test, the Iowa Medial Consonant Test, and the City University of New York (CUNY) Sentences Test. All three tests were presented using the Iowa Audiovisual Speech Perception Tests Video Laserdisc. Each test was presented in three different conditions: sound alone, vision alone and sound-plus-vision. Lipreading enhancement was assessed by comparing each subject's score in the vision-alone test condition to the corresponding score in the sound-plus-vision condition.

> *The Iowa Medial Vowel Test* is a measure of closed-set phoneme identification and consists of eight vowels presented in a /hVd/ context. The eight medially placed vowels were presented three times (24 total items) in a randomized order.
>
> *The Iowa Medial Consonant Test,* an additional measure of closed-set phoneme identification, features 16 consonants in an /aCa/ context, each of which was repeated five times in random order (80 total items).

The City University of New York (CUNY) Sentence Test consists of 72 lists of sentences. Each test list consists of 12 sentences, varying in length between three and 14 words. The test was scored according to the total number of correctly recognized words (102 words per list) and was presented in an open-set format.

Performance and Final Questionnaires: The Performance and Final Questionnaires were developed by the sponsor as subjective measures of device benefit. The Performance Questionnaire was administered to recipients following three-to-six months of device use, and the *Final Questionnaire* was administered just prior to PMA submission.

7. Effectiveness Data

As is customary for single-subject research designs, study results were analyzed for each subject individually. For each of the sound-alone measures (i.e., recorded measures of environmental sound identification, pattern perception, closed-set word identification and open-set sentence recognition), the binomial model was applied to each subject's postoperative test score, to determine whether the individual's test score was significantly above chance. With respect to the three measures of lipreading enhancement, the binomial model was used to evaluate whether a given subject's score improved significantly when using the ABI in conjunction with lipreading, compared to his or her performance using lipreading alone. The binomial tests were both one- and two-tailed (sound alone and lipreading enhancement measures, respectively) and probability values of 0.05 or less were required for statistical significance.

Claims of device effectiveness are based on recorded tests of familiar environmental sounds, recorded speech perception tests, audio-visual performance measures, and on results reported in the final questionnaire. With very few exceptions, each outcome measure was administered postoperatively to all 60 subjects to assess the effectiveness of the Nucleus ABI system. Although not all subjects completed and returned the final questionnaire (44 out of 60), subjective outcomes were, nonetheless, well represented for the majority (73.3%) of the sample. Each of the following therapeutic claims is based on the number of patients tested using a particular outcome measure, or on the number of questionnaire respondents, respectively.

Results of Clinical Studies:

a. Effective Auditory Stimulation

- Eighty-two percent (72/90) of the implanted subjects were able to perceive sound and use the device postoperatively.

b. Identification of environmental sounds

- Eighty-two percent of the subjects (49/60) scored significantly above chance (43%) on a recorded, closed-set test of environmental sound identification.

- Using the ABI, subjects recognized 53.9% of common environmental sounds, on average, and 65% of the sample (39/60) recognized 50% or more of the sounds.

c. Lipreading enhancement

- Eighty-five percent of the tested subjects (49/58) demonstrated statistically significant improvements in open-set sentence understanding, when using the ABI in conjunction with lipreading.

- The average sentence recognition score improved from 31.2% for lipreading alone, to 53.5%, when subjects combined auditory information from the ABI with lipreading.

d. Open-set sentence recognition

- Using sound alone, 12% of study participants (7/58) scored greater than 10%, on a difficult open-set test of sentence understanding.

e. Questionnaire results

- Sixty-one percent of the subjects (19/31) who received the device following removal of their second-side tumor (31 of the 44 respondents), reported using the ABI on a daily basis for ten or more hours.

- Eighty percent (35/44) of the respondents reported receiving benefit from the auditory brainstem implant and 84% indicated that the decision to get the ABI was the right one.

- Seventy-three percent (32/44) of the respondents would recommend an ABI to others.

8. Statistical Analyses

The 60 ABI recipients were studied using a repeated measures, single-subject research design. Postoperative device benefit was evaluated for each individual subject on a variety of outcome measures, using the binomial statistical model. Postoperatively, scores on measures of environmental sound identification and closed- and open-set speech perception were compared to chance performance levels. Similarly, postoperative scores obtained with lipreading were compared to test scores obtained by each subject, when lipreading was augmented with sound from the ABI. In this way, each subject was established as his or her own experimental control, and constituted an independent replication of the experiment. The strength and consistency of the investigational findings across the 60 replications provided evidence that the investigational findings were generalized to the larger population of adult and adolescent ABI recipients.

Experimental hypotheses were tested using three inferential statistical models. The binomial model was used to evaluate whether the percentage of items, passed by a single subject on a particular test measure, was significantly above chance. The binomial model also was used to determine whether two percentage scores, obtained by a single subject in two different test conditions (lipreading alone and lipreading-plus-sound) were significantly different. For sound-alone test measures, 95% confidence intervals were calculated around the proportion of subjects scoring significantly above chance, postoperatively.

In addition to the inferential models, well-known descriptive statistics were used to characterize the investigational sample and standardized measures of incidence were applied to the safety data.

IX. CONCLUSIONS DRAWN FROM STUDIES

Ninety teenagers and adults with Neurofibromatosis Type 2, implanted with the Nucleus Auditory Brainstem Implant System, were studied for device safety, and 60 were studied for device effectiveness.

For each of the 60 effectiveness subjects, overall device benefit was defined as either a statistically significant enhancement of lipreading on CUNY Sentences with device use, or a significantly above-chance score on two or more of the five tests administered sound-alone. Even when using this rather conservative definition of device benefit, 95.0% of the investigational subjects (57/60) received statistically and clinically significant benefit from the ABI.

For the 90 subjects studied for safety, there were no device failures during the course of the study. However, 16 of these 90 subjects did not receive auditory stimulation from the device, postoperatively, either due to migration or surgical misplacement of the electrode array. All other medical/surgical and device-related complications were characteristic of cochlear implantation and/or acoustic

tumor removal surgery in general, and were not unique to the investigational device. All complications were closed or resolved during the course of the study, with no life-threatening, hazardous, or permanent side effects due to the device.

The results of the preclinical and clinical studies provide reasonable assurance of the safety and effectiveness of the Nucleus 24 Auditory Brainstem Implant System. Although the potential exists for minor differences in physiological response by gender for the target population, the minimal number of clinically significant findings does not indicate that gender differences are of clinical importance for this device.

X. PANEL RECOMMENDATION:

At an advisory meeting held July 21, 2000, the Ear, Nose and Throat Devices Panel recommended that the Cochlear Corporation's Nucleus 24 Auditory Brainstem Implant System be approved with conditions. These conditions included changes to the device labeling and a recommendation for the implant team to be trained in the techniques used for appropriate implantation.

XI. FDA DECISION

Expedited processing was authorized on July 14, 2000 since no other alternatives following tumor removal exist to treat the intended patient population.

The manufacturing facility was found to be in compliance with device Good Manufacturing Practices (GMP). The following manufacturer and sterilizer sites were inspected:

Cochlear Ltd, Sydney, Australia, June 10, 1999;
Griffith MicroScience, Salt Lake City, UT, December 17, 1998
Parter Medical Products, Carson, CA, June 29, 2000.

Final GMP approval was dated August 25, 2000.

After the Panel meeting, FDA completed the review of the Surgeon's Manual and worked with the sponsor to finalize product labeling. The product labeling was written to address the concerns discussed by the Advisory Panel.

FDA issued an approval order on October 20, 2000.

XII. REFERENCES

1. Brackmann D. E., et al., "Cochlear Implants and Auditory Brainstem Implants", draft 19 December 1997;
2. Dymond A. M. et al., "Brain tissue reaction to some chronically implanted metals", J. Neurosurgery / Volume 33 / Nov. 1970;
3. Liu X., et al., "Acute study on the neuronal excitability of the cochlear nucleus of guinea pig following electrical stimulation", Acta Oto-Laryng. (Stockh) 117: 363-375, 1997;
4. Liu X., et al., "Histologic and Physiologic effects of the central auditory prosthesis surface versus penetrating electrode", Hearing Research 114: 264-274, 1997;
5. Liu X., et al., "Acute study on safety and efficacy of an auditory brainstem prosthesis", Acta Oto-Laryng. (Stockh): 118(1): 37-45, 1998;
6. Liu X., et al., "Chronic study on neuronal excitability of the cochlear nuclei of the cat following electrical stimulation", Acta Oto-Laryng. (Stockh): 1997, In press;
7. McCreery D. B., et al., "Charge density and Charge per Phase as Cofactors in Neural Injury Induced by Electrical Stimulation", IEEE Transactions on Biomedical Engineering, Vol. 37, No.10, Oct. 1990;
8. Manrique M, et al.., "Experimental Study following Inactive Implantation of an Auditory Brainstem Implant in Monkeys", Pamplona, Spain, In press;
9. Manrique, M. et. al., "Normal neuronal pattern and changes after deafferentization of cochlear nucleus in monkeys", XVI Congress of Otorhinolaryngology Head and Neck Surgery, Sydney, 2-7 March 1997;
10. McCreery, D. B. et. al., "Stimulation with chronically implanted microelectrodes in the cochlear nucleus of cat: Histologic and physiologic effects", Hearing Research 62 (1992) 42-56;
11. Brummer, S. B. et Turner, M. J., "Electro-chemical considerations for Safe Electrical Stimulation of the Nervous System with Platinum Electrodes", IEEE Transactions on Biomedical Engineering, Jan 1997;
12. Terr, L. I., "Biocompatibility of the central electroauditory prosthesis and the human cochlear nuclei", The American Journal of Otology, Vol. 10, No. 5, Sept. 1989;
13. Brackmann D. E., et al.., "Auditory Brainstem Implant: I. Issues in surgical implantation", Otolaryngol Head Neck Surg 1993: 108;
14. Shannon R. V., et al.., "Auditory Brainstem Implant: II. Postsurgical issues and performance", Otolaryngol Head Neck Surg 1993: 108;
15. Shannon RV, "A model of Safe Levels for Electrical Stimulation", IEEE Transactions on Biomedical Engineering, Vol. 39, No. 4, April 1992;
16. Manrique M, et al., "Auditory Brainstem Implant: Experimental Research Project in Monkeys. Preliminary Report: group D", University of Navarra, Pamplona, Spain;

17. Rose, TL, et al., "Electrical Stimulation with Pt Electrodes. VIII. Electrochemically Safe Charge Injection Limits with 0.2ms Pulses", IEEE Transactions on Biomedical Engineering, Vol. 37, No. 11, November 1990;
18. Paul Carter, "In Vivo Direct Current Measurements for High Stimulation Rates", Cochlear Limited Technical Memo Ref. No. TM 0111, 1996.