FDA Executive Summary

Prepared for the
November 8, 2013 meeting of the
ENT Devices Panel

Premarket Approval
P130016

Cochlear Corporation
Nucleus Hybrid L24 System

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1. Introduction

The information in this document comprises FDA's executive summary of premarket approval (PMA) application P130016 from Cochlear Americas for the Nucleus® Hybrid™ L24 Implant System, which is also referred to throughout this document as the Hybrid L24. Included are a description of the device, a brief summary of the pre-clinical testing information, a summary of related non-pivotal clinical studies, and a description of the pivotal clinical investigation conducted by Cochlear Americas (a description of the clinical study protocol and its endpoints, results, and statistical analyses).

The Hybrid L24 is a first-of-its-kind system designed to provide electrical and acoustical stimulation simultaneously to the patient who has significant low-frequency residual hearing but has severe to profound hearing loss in the mid- and high-frequency regions of hearing. An external sound processor delivers electrical stimulation to the mid- and high-frequency regions of the cochlea through a relatively short (16-mm in length) intra-cochlear electrode array. The same processor also delivers acoustic amplification (similar to traditional hearing aids) to the low-frequency regions of the cochlea for patients with aidable low-frequency residual hearing.

The Hybrid L24 shares several similarities in design with all currently approved cochlear implant device systems which are indicated for patients 12 months of age or older. Specifically, the Hybrid L24 includes an external sound processor and a surgically implanted electronic device with an electrode array. The electrode array is inserted into the cochlea and electrically stimulates the spiral ganglion cells which innervate the auditory nerve fibers, thereby bypassing the damaged sensory hair cells of hearing impaired patients.

The Hybrid L24 differs from traditional cochlear implant devices in the following ways: (1) the proposed indications for use for the Hybrid L24 includes patients with acoustically aidable residual low-frequency hearing, (2) the proposed indications for use for the Hybrid L24 restricts the patient population to individuals aged 18 and older, (3) the electrode array is shorter in length for the Hybrid L24 than traditional cochlear implant arrays offered by Cochlear Americas, and (4) the Hybrid L24 includes an acoustic component as part of the external sound processor to provide amplification of low-frequency sounds for the indicated patients who are expected to have acoustic hearing sensitivity post implantation.

2. Device Description

The Hybrid L24 is an electric-acoustic stimulation (EAS) cochlear implant system intended to address the needs of individuals who demonstrate residual low-frequency hearing sensitivity, but who have severe to profound mid and high-frequency sensorineural hearing loss. The Hybrid L24 provides electric stimulation to the mid- to high-frequency regions of the cochlea through a cochlear implant, and for patients with

aidable residual low-frequency hearing sensitivity following implantation, acoustic amplification is provided to the low-frequency region. Together, the internal and external components compose the Hybrid L24 system. The following sections describe the system components in further detail.

2.1 Nucleus® Hybrid™ L24 implant

The Hybrid L24 implant consists of the Nucleus CI24RE receiver / stimulator assembly with the Hybrid L24 electrode array, and an extracochlear ground electrode. The receiver/stimulator is unchanged from the approved Cochlear Nucleus® Freedom™ cochlear implant (model CI24RE "Freedom" receiver/stimulator subassembly, approved under PMA supplement P970051/S028). However, the Hybrid L24 implant includes a new intracochlear electrode array to the CI24RE receiver/stimulator assembly. The faceplate on the implant includes a new embossing for the Hybrid L24 implant array ("CI24REH"). The Hybrid L24 implant is shown in Figure 1.

The Hybrid L24 electrode array has 22 active electrodes as do the three currently approved arrays for the CI24RE assembly: the conventional straight (ST) array, the thin straight array (termed "CI422"), and the pre-curled, modiolus-hugging Contour Advance (CA) array. The Hybrid L24 is a straight array that is shorter and/or thinner than these approved arrays and designed to reach only the more basal regions of the cochlea, as shown in an image in Figure 2. The Hybrid L24 array is designed to preserve the integrity of the more apical region of the cochlea which mediates low-frequency hearing. The Hybrid L24 array is therefore designed to increase the likelihood of retaining residual low-frequency hearing sensitivity following implantation. It is designed to have the smallest insertion depths (of 15 to 16 mm, or 250 to 270 degrees) when compared to the three aforementioned, approved arrays. In contrast, the CI422 array can be inserted to depths up to 25 mm (or 420 degrees). Photographic comparison of the approved CI422 array and the Hybrid L24 array is shown in Figure 3. Note the shorter length and the larger stopper of the Hybrid L24 array, both of which limit the insertion depth compared to the CI422 array.

2.2 Nucleus 6 (CP900 series) sound processor and other external components

The Hybrid L24 uses the following key external components: CP900 series Sound Processor (and accessories), CR200 series Remote Assistant, and Custom Sound Suite v4.0 software.

The CP900 series (of Nucleus 6) of sound processors includes the CP910 and CP920 Sound Processors (shown in Figure 4). Similar to the sound processors of currently approved cochlear implant systems, including the applicant's CP810 (electrical stimulation only), the CP910 and CP920 process sound to provide electrical stimulation to the electrode array. In addition, as part of the Hybrid L24 system, the CP910 and CP920 can also process sound to provide amplified acoustic sound in the specified, low-frequency acoustic region through the use of an included Acoustic Component (EAC200 series power speaker unit) that fits into the concha and canal of the outer ear. The

Acoustic Component (with CP910) is shown in the bottom panel of Figure 4. Thus, EAS is provided to the ipsilateral ear for the patient through a single sound processor.

The CP920 omits the Accessory Connector for connecting to various audio accessories from the CP910 to decrease the overall size of the CP920. Otherwise, the CP910 and CP920 are identical.

The Custom Sound v4.0 fitting software includes the necessary new functionality to provide EAS for patients, including the ability to enter a low-frequency audiogram, split the acoustic / electric frequency regions, and specify the fitting prescription method, acoustic amplification gains, and compression method.

2.3 Device system used in pivotal Investigational Device Exemption (IDE) study

Due to the fact that the clinical trial was completed over a period of five years, the Freedom Hybrid Sound Processor used in the pivotal IDE study (G100971) is no longer being marketed or produced. The older Freedom Hybrid Sound Processor that was used in the IDE clinical study will be replaced by the Nucleus 6 Sound Processor (i.e., the CP900 series sound processor), which also permits acoustic amplification.

Reviewer Comment: *The applicant provided bench verification testing in the PMA demonstrating that the Nucleus 6 (CP900) series of sound processors (proposed for marketing) has similar acoustic and electric output to the Freedom Hybrid processor (used in the clinical study). This testing is summarized in section 5.4 below. FDA has reviewed this information and finds it acceptable.*

3. Proposed Indications for Use

The Hybrid L24 is indicated for the following individuals:

- Patients 18 years or older who have residual low-frequency hearing sensitivity and bilateral severe to profound high-frequency sensorineural hearing loss, and who obtain limited benefit from bilateral hearing aids.

- Typical preoperative hearing loss of candidates ranges from normal to moderate hearing loss in the low frequencies (thresholds no poorer than 60 dB HL at ≤ 500 Hz), and from severe to profound hearing loss at frequencies above 1500 Hz (threshold average of 2000, 3000, and 4000 Hz ≥ 75 dB HL).

- 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.

The audiogram range for the subjects who were included in the pivotal study as per the above indications is illustrated in Figure 5.

Reviewer Comment: *The applicant's proposed age indication for the Hybrid L24 is 18 years or older. However, the youngest subject enrolled in the pivotal study (G070191) was 23 years of age at the time of implantation (only one subject), while all other study subjects were older than 36 years. The applicant states in the PMA that even though there were no Hybrid L24 subjects within the age range of 18-22 years enrolled during the study, there is longstanding evidence that this age group has not shown any specific vulnerability or risk with regard to their outcomes (effectiveness or safety) in cochlear implantation, and, therefore, wishes to retain their proposed indication for patients 18 years or older. The Advisory Panel will be asked to comment on whether the data from the pivotal study (which included only subjects 23 years or older) supports the approval of the Hybrid L24 for patients as young as 18 years of age. Given the lack of data for subjects less than 23 years old, and the limited data for the younger adult population (i.e., one study subject in their twenties), FDA would like the Panel members to discuss whether they believe there is sufficient information to extrapolate the use of this product to patients 18 years or older.*

4. Regulatory History

4.1 IDE Studies

Prior to initiating the pivotal clinical study for the Hybrid L24, the applicant initiated two IDE studies (G990155 and G070016) aiming to assess the safety and effectiveness of hybrid or electric-acoustic stimulation (EAS) with shorter than the current FDA-approved electrode arrays. G990155 was approved in 1999 as a feasibility study for a single study site and was later expanded to a multicenter study with a modified device. Initially, G990155 studied a 6-mm array with 6 contacts, which was subsequently modified to a 10-mm array (also with 6 contacts). The applicant closed G990155 in 2011. The second ongoing study G070016, approved April 9, 2008, continues to investigate the Hybrid S12 device with a 10-mm array with 12 electrode contacts; this study is still ongoing. Study description and results from G990155 and G070016 are further described below in Section 6.

The pivotal clinical study supporting this original PMA was conducted under IDE G070191 which was approved April 9, 2008. Per the applicant's protocol, the purpose of the study was to further explore the optimal combination of insertion depth and number of electrodes or channels in a hybrid device. The Hybrid L24 implant with the predecessor Freedom Hybrid sound processor was studied. The trial was conducted from 2007 to 2012 for the collection of effectiveness endpoint data while safety data collection is still ongoing per the applicant's study protocol for G070191 which states, "The primary endpoint of the study for device efficacy is the 6 month postactivation evaluation. Subjects will remain in the study with semi-annual evaluations, until Sponsor formally closes the study."

G070191/S026: Under Supplement 26 for the G070191 IDE, approved on July 17, 2013, the applicant is currently investigating new noise reduction and environmental classification features in the existing pivotal study cohort using the next generation CP900 processor. A summary of these features follows:

- Signal-to-Noise Ratio-Noise Canceller (SNR-NC): This feature is designed to estimate the signal-to-noise ratio (SNR) in each spectral channel using the currently available Advanced Combination Encoder (ACE) strategy. Noise removal (cancellation or reduction) is achieved by suppressing the content of any channels with negative SNRs to ensure that they are not used in stimulation, while passing the content of channels with positive SNRs.

- Wind noise reduction (WNR): This feature is designed to detect and cancel/reduce low-frequency wind noise for enhanced listening comfort for recipients.

- Environmental Classifier (EC) also known as SCAN: The EC feature attempts to automatically classify incoming sound / the listening environment and adjust the sound coding algorithm to match the listening environment per the following choices: Everyday (default), Noise, Focus (directionality) and Music.

4.2 Pre-Market Approval Applications

On August 2, 2013, under Supplement 96 of P970051, the applicant received approval for the Nucleus 6 series of sound processors, i.e., the CP900 series of sound processors. This approval is for the sound processor without the acoustic component contained in the Hybrid L24 and for use with the applicant's currently approved cochlear implants [CI24RE (ST), CI24RE (CA), CI422].

The applicant submitted the current original PMA (P130016) for the Hybrid L24 device system (with CP900 series of sound processors with the Acoustic Component) on June 3, 2013.

5. Pre-Clinical Studies

The applicant provides information and testing in the following areas for the Hybrid L24 implant: biocompatibility, sterilization, packaging, and shelf life, and the manufacturing processes for the electronic and final assembly.

Reviewer Comment: *FDA reviewers found this information and testing to be adequate.*

Further summaries of pre-clinical testing are provided in the following sections.

5.1 Software validation

The applicant states that the Custom Sound (version 4.0) fitting software will be released with the Hybrid L24 implant system. This fitting software permits programming of both the acoustic and electric components of the CP900 series sound processor. Sound processing strategies and pre-processing features that are already approved and consistent with strategies / features used in the Hybrid L24 clinical trial will be available. Software verification and validation was submitted by the applicant.

Reviewer Comment: *FDA reviewers found this information adequate.*

5.2 Magnetic resonance imaging compatibility

The applicant states that the Hybrid L24 Implant uses the same stimulator package, electronic assembly, coil assembly, and implant magnet as the approved CI24RE implant. The electrode length is similar in length to the Contour Advance and Straight electrodes, and the array is essentially a shorter version of the approved CI422 electrode array. The proposed MRI labeling (i.e., MR Conditional) is the same as that approved for the CI422, and repeated MRI testing was not deemed necessary by the applicant.

Reviewer Comment: *The applicant's rationale for MRI testing/labeling have not been found to be adequate by FDA reviewers. This issue can likely be resolved through further testing and/or appropriate labeling.*

5.3 Electromagnetic compatibility

Based on similar designs of the receiver / stimulator, leads, and array between the CI24REH and the approved CI24RE (CA) or (ST), the applicant provides a rationale that electromagnetic compatibility (EMC) for the CI24REH is equivalent to levels of the approved implants for which testing was previously submitted. EMC testing was submitted for the CP900 sound processor.

Reviewer Comment: *The applicant's EMC testing and rationale is under FDA review. If needed, this issue can likely be resolved through appropriate labeling.*

5.4 CP900 acoustic and electric output verification

As discussed in Section 2.3, the applicant submitted bench testing verification to show that the acoustic and electrical output of the CP900 series is functionally comparable to the Freedom Hybrid sound processor (note: the external Freedom Hybrid sound processor was used during the pivotal IDE study). Four sets of tests were conducted:

1. Measurement of amplification characteristics of the acoustic component using accepted air-conduction hearing-aid metrics: e.g., output sound pressure level for a 90 dB SPL input [OSPL90], full-on gain, total harmonic distortion, automatic gain control characterization, input-output characterization (including measurement of compression ratios), etc.

2. Verification that the acoustic component provides appropriate and accurate gains for indicated patients. In testing of 4 audiograms selected as representative sample of differing hearing loss profiles, measured gains were all within 5 dB of target gains for all frequencies tested and compression settings.

3. Speech processing- electrical and acoustical path verification using representative speech tokens:
   a. electrodogram outputs for the electrical path
   b. acoustical spectrograms for the acoustic path.

4. Acoustical path – Long term average speech spectrogram.

Reviewer Comment: *FDA reviewers found these methods and test results adequately show that the CP900 series sound processor (proposed for marketing) provides comparable acoustic and electric output to the Freedom Hybrid sound processor.*

5.5 Hybrid L24 mechanical testing

5.5.1 Temporal bone testing of electrode array

Hybrid L24 electrodes were inserted into 18 temporal bones by a standard posterior tympanotomy approach and subsequently processed for histological assessment which showed no evidence of trauma.

Results also showed (1) minimal resistance when inserting the electrode, (2) full insertion depth could be achieved with a single stroke insertion, and (3) the electrode did not buckle in the proximal region.

Reviewer Comment: *FDA reviewers found the methods and testing adequate.*

5.5.2 Mechanical and environmental testing

As the Hybrid L24 implant uses the same stimulator and coil assembly as the CI24RE cochlear implant, the applicant states that environmental tests performed on the CI24RE may be applied with confidence to the Hybrid L24 implant. The only difference between the two implants (the intra-cochlear electrode array) reportedly had no possible impact on the environmental test results.

The Hybrid L24's intra-cochlear electrode array was subjected to the following mechanical robustness bench testing:

- Multiple insertion testing
- Linear and angular fatigue test of the electrode array
- Severe stress and twist of the electrode lead
- Severe electrode lead shear test

Reviewer Comment: *FDA reviewers found the methods and testing adequate.*

6. Related Clinical Studies

6.1 G990155 (Hybrid 6) study

The applicant initiated a single-site feasibility study in 1999 (approved under G990155) at the University of Iowa. Three subjects were implanted with a 6-mm array with 6 electrode contacts based on the CI24M receiver/stimulator. In 2000, the applicant requested and received approval to modify the electrode length from 6 mm to 10 mm with the same number of contacts to determine if better results could be achieved with a somewhat longer array. In 2002, the applicant received FDA approval through an IDE supplement to expand the feasibility study into a multicenter study, in order to determine if the initial results from the University of Iowa could be generalized to other study sites. This stage is referred to as the 'Phase I trial.' During this phase, 25 subjects received the 10-mm array, CI24M-based device called the Hybrid 6. In 2005, this study was expanded to a total of 21 sites in order to further broaden surgical and clinical experience. In addition, the device design was altered to incorporate the existing 10-mm electrode array with the current-generation Nucleus Freedom (CI24RE) receiver stimulator. This is referred to as the 'Phase 2 trial.' Under Phase 2, 58 subjects received Nucleus Freedom-based 10-mm array devices.

The final summary of studies under G990155 included 87 subjects implanted with the 10-mm electrode design. The mean age of the subjects was 58.9 years with a range of 19-82 years. Subjects are reported to generally demonstrate significantly improved scores on word recognition in quiet and sentence recognition in quiet and in noise. The applicant concluded that the medical/surgical and device-related effects that occurred in this IDE study were consistent with cochlear implantation in general, and not unique to the Nucleus Hybrid 6 implant. In all, 107 medical/surgical and device-related effects occurred during the study and, out of those, 78 were resolved during the course of the study with no life threatening, hazardous or permanent side effects. Of the 29 cases that were not resolved before the conclusion of the study, there were: 10 cases of complete loss of low-frequency hearing, 9 cases of tinnitus, 3 cases related to a perceived sound quality problem, 2 cases of lightheadedness or vestibular symptoms, 2 cases of poor or decreased performance, one case of taste disturbance, one case of ear infection, and one case of scalp pain/tenderness. It is also important to note that the data in the final report for G990155 revealed that, of the 87 subjects, 17 were reimplanted with a traditional cochlear implant.

6.2 G070016 (Hybrid S12) study

The applicant proposed a study in G070016 (approved in 2008) to assess if better results could be achieved with more electrode contacts/channels. The device is the Hybrid S12 and the electrode array is a 10-mm Hybrid array with a greater number (12) of electrode contacts than the device studied in G990155. As of December 31, 2012, 57 subjects ranging from 41-86 years of age had consented to be evaluated for participation in the study. Of these 57 subjects, 24 have been implanted with a Nucleus Hybrid S12.

The G070016 was proposed with identical single-subject, repeated-measures design, as with that in G070191, and was comprised of identical safety and effectiveness measures as proposed in G070191. The study under G070016 is still on going, and the data submitted in the most recent annual progress report revealed that, of these 57 subjects, 24 have been implanted with a Nucleus Hybrid S12. Further, of the 24 subjects, 8 (33%) had exhibited a more than 30-dB loss in their residual low-frequency hearing in the implanted ear. The available data for the effectiveness measures indicated that the subjects performance at the 6-month interval improved from their preoperative, baseline performance.

6.3 Australian Clinical Study

Beginning in 2005, a clinical study on the Hybrid L24 was initiated at The Hearing Cooperative Research Center (CRC) in Melbourne, Australia. The objective of this early stage study was to investigate the hearing preservation and benefit of providing acoustic-electric stimulation to individuals with low-frequency hearing and severe-to-profound high-frequency hearing loss via implantation of the Hybrid L24. Thirteen subjects were enrolled and implanted, with one withdrawal (due to advancing Alzheimer's symptoms). Results at activation revealed that 9 of the 13 subjects had a mean change in hearing thresholds from preoperative of $\leq$ 15 dB. Over the next 12 months at different time points (6 months, 9 to 10 months and 12 months) there were three subjects who experienced a significant shift in hearing. At the twelve month interval, 9 of 12 subjects saw a shift in hearing of $\leq$ 30 dB HL while 8 of 12 experienced only a shift of $\leq$ 15 dB. For speech intelligibility, group mean measures using analysis of variance showed a significant improvement in each of the testing conditions when comparing preoperative to the 12-month postoperative test interval. For the monaural condition using the word stimuli, the mean preoperative (acoustic hearing aid in implant ear) score of 8% was in contrast to the Hybrid (electric and acoustic stimulation in implant ear only) group mean score postoperatively of 35.8%. In the Combined condition (electric + acoustic stimulation in implant ear combined with acoustic stimulation in the non-implant ear), the preoperative (bilateral hearing aids) score of 16.4% was in comparison to the group mean score of 40.8% at the 12 month interval. Also, in the combined condition, with the stimuli (sentences) presented in noise, a significant improvement was also detected with a group mean preoperative score of 43% and a postoperative score at 12 months of 70.4%.

Six subjects experienced adverse events with one withdrawing (due to Alzheimer's disease). One subject experienced labyrinthitis accompanied by hearing loss requiring

hospitalization. The remaining four subjects experienced temporary events consistent with cochlear implant surgery and all resolved by the end of the study. The applicant concluded that Hybrid L24 presents potential for use in preserving hearing and improved speech outcomes for the majority of subjects, postoperatively.

6.4 European Clinical Study

In 2006, the applicant initiated a multi-center study (16 centers) in the European Union to support the application for the CE mark of the Hybrid L24. Subjects were 66 adults (aged 21 to 81) implanted with the Hybrid L24 and receiving electric-acoustic stimulation (EAS). There were two study objectives: (1) to measure the preservation of residual hearing in subjects who receive the Hybrid L24 implanted through the round window and (2) to assess the post-operative performance of the subjects in their 'best-aided condition' as compared to their best-aided preoperative performance.

This clinical study was a single-subject, repeated-measures design that enrolled subjects with bilateral hearing loss. Specifically, hearing thresholds were in the mild to moderate range in the low frequencies, sloping to a severe-to-profound high-frequency sensorineural hearing loss. Subjects were required to have used hearing aids a minimum of six weeks prior to enrollment in the study. Of the 66 subjects enrolled and implanted, 64 had insertion via round window, the remaining two via cochleostomy. Sixty-one (61) subjects completed the 12-month post-operative study duration. Results revealed that at activation, 89% of low-frequency thresholds (125, 250 and 500 Hz) were preserved within 30 dB of preoperative thresholds (n = 66). At 12 months postoperatively, 73% showed thresholds decreased $\leq$ 30 dB at 500 Hz and 43% were $\leq$ 10 dB at 500 Hz (n = 61), and 73% of subjects improved by at least 20% on their speech recognition scores in noise. The mean benefit for speech in quiet (postoperative score minus preoperative score) was 23% for the implant ear. Forty-four of the subjects were evaluated for listening in noise, and results revealed a 31% mean benefit for the implant ear. For centers that chose to evaluate an adaptive SNR, a 6.1 dB median benefit was found for the implant ear. Finally, the applicant notes that there were also significant benefits of the Hybrid implant shown with questionnaire data (Speech, Spatial, and Sound Qualities Questionnaire [SSQ] and Health Utilities Index [HUI]).

Twelve adverse events were reported over the course of the study. Seven were serious events, and four were related or possibly related to the device or surgery. All seven were resolved. The study concluded that the Hybrid implant with the Freedom Hybrid sound processor had been proven beneficial for subjects with residual hearing in their implant ear.

Reviewer Comment: *Any conclusions or comparisons between the outside-US studies, other US IDE studies and the pivotal US IDE study are limited due to differences in the enrolled study populations and differences in study design.*

7. Pivotal Clinical Study

7.1 PMA Cohort Clinical Study Protocol Summary

7.1.1 Study Overview

The applicant performed an IDE (G079191) pivotal clinical trial to study the safety and effectiveness of the Hybrid L24 from 2007 to 2012. This study had a prospective, multi-center, non-randomized, repeated–measures design. Fifty subjects with severe to profound high-frequency loss and significant levels of low-frequency acoustic hearing, were implanted across 10 clinical sites. Subjects served as their own controls.

There were a total of 5 pre- or post-implant test conditions: Acoustic Alone (acoustic stimulation to the ear to be implanted), Bilateral Acoustic (acoustic stimulation to both ears), Hybrid (simultaneous electric and acoustic stimulation using the Hybrid L24 implant and acoustic component in the implanted ear), Bimodal (electric stimulation only using the Hybrid L24 implant and contralateral acoustic stimulation), and Combined (electric and acoustic stimulation using the Hybrid L24 implant with acoustic component in the implanted ear and contralateral acoustic stimulation). The Acoustic Alone and the Bilateral Acoustic conditions are pre-implant (i.e., baseline) conditions. Table 1 illustrates the three possible post-implant test conditions: Hybrid, Bimodal and Combined.

For the Acoustic Alone and Hybrid conditions, the contralateral ear was plugged during speech perception testing. For the Bimodal condition, the ipsilateral ear was plugged during speech perception testing. Ipsilateral acoustic testing (i.e., Acoustic Alone, Hybrid, and Combined conditions) was not performed if a subject exhibited a profound/total loss of residual low-frequency hearing.

Subjects and investigators were not blinded to the device mode, as it is not possible to conceal the presence or absence of a cochlear implant. Subjects were assessed audiometrically and for effectiveness measures preoperatively, postoperatively at device activation, and at 3, 6, and 12 months postactivation of the implant. Subjects were also asked to attend follow-up audiometric evaluations biannually following the 12-month evaluation.

The primary and secondary effectiveness endpoints were measured at 6 months postactivation, with subjects listening unilaterally in the Hybrid condition and performance was compared with the preoperative Acoustic Alone performance. For subjects whose residual low-frequency hearing sensitivity degraded to the profound or total hearing loss levels (thereby precluding acoustic amplification with the Hybrid sound processor), the applicant still included these data under the “Hybrid” condition even though these subjects actually listened only electrically through the implant portion of the device. Additional exploratory analyses conducted by the applicant involved assessment

of the subjects' performance using the device in the Combined or Bimodal condition that reflect the typical manner in which the device is used on a daily basis.

7.1.2 Study Objective and Endpoints

7.1.2.1 Study Objective

The objective of this study was to evaluate the safety and effectiveness of the Hybrid L24 electric-acoustic cochlear implant system in individuals with residual low-frequency hearing (no worse than a moderate loss) and bilateral severe-to-profound high-frequency (above 1500 Hz) sensorineural hearing loss.

7.1.2.2 Safety Endpoints

The primary safety endpoint was defined as any surgical and/or device-related event, reported as the number and proportion of individuals experiencing an adverse event. The adverse events include anticipated and unanticipated adverse events. The applicant did not propose formal hypotheses for the safety endpoint.

7.1.2.3 Co-Primary Effectiveness Endpoints

(1) CNC Word Recognition (as described in 7.1.7.2.1) – The endpoint was to compare between preoperative CNC word scores in Acoustic Alone condition (acoustic stimulation alone in the ear to be implanted) and 6-month postactivation CNC word scores for the implanted ear in the Hybrid condition (acoustic and electric stimulation in the implanted ear). The null hypothesis tested was that there was no difference between subjects' pre- and postoperative speech performance, as measured by the CNC Word Recognition Test, at the 6-month interval.

(2) AzBio Sentence Recognition in Noise (as described in 7.1.7.2.2) – The endpoint was to compare between preoperative AzBio sentence scores in the Acoustic Alone condition and 6-month postactivation scores for the Hybrid condition. The null hypothesis to be tested was that there was no difference between subjects' pre- and postoperative speech performance, as measured by AzBio sentences in noise.

7.1.2.4 Secondary Effectiveness Endpoints

Secondary effectiveness endpoints are based on the post-operative performance in the Hybrid condition and they are described as follows:

- On the CNC word recognition test, most (> 75%) of the subjects scored equal to or better than they did in the preoperative ipsilateral Acoustic Alone condition;

- On the CNC phoneme recognition test, most (> 75%) of the subjects scored equal to or better than they did in the preoperative ipsilateral Acoustic Alone condition; and

- On the AzBio sentences-in-noise test, most (> 75%) of the subjects scored equal to or better than they did in the preoperative ipsilateral Acoustic Alone condition.

The applicant proposed no formal statistical hypothesis testing for the secondary effectiveness endpoints.

7.1.2.5 Additional Test Condition (Combined condition)

The CNC Word Test and AzBio sentences-in-noise test scores were assessed in the Combined condition at 6 months postactivation, compared to subjects' pre-operative baseline performance under the Bilateral Acoustic condition. The intent of these analyses was to determine device effectiveness when the Hybrid L24 is used in conjunction with acoustic hearing in the contralateral, non-implanted ear, as this listening mode is used on an everyday basis by subjects according to the applicant.

7.1.3 Additional Effectiveness Measures

Several additional measures were adopted to study effectiveness in a various functional aspects other than subjects' word and sentence recognition abilities. The SRT in Noise Test (as described in 7.1.7.2.3) was administered to examine speech perception in spatially separated noise in the best listening modes. The University of Washington Clinical Assessment of Music Perception (UW-CAMP as described in 7.1.7.2.4) was administered to compare subjects' music perception performance in the Hybrid and Combined conditions at 6 months postactivation with their pre-operative baseline performance in the ipsilateral and bilateral acoustic conditions, respectively. The applicant states that the intention of these analyses is to demonstrate the usefulness of preserving low-frequency acoustic hearing in Hybrid cochlear implant recipients.

In addition, three patient-reported questionnaires, i.e., the Speech, Spatial and Sound Qualities (SSQ) questionnaire, Device Use Questionnaire (DUQ), and Musical Background Questionnaires (MBQ) were administered pre- and post-operatively in the everyday listening mode (i.e., Bimodal or Combined) to assess various functional aspects of device effectiveness for the Hybrid L24 when used in the Combined condition. The SSQ, DUQ, and MBQ questionnaires are described in sections 7.1.7.2.5, 7.1.7.2.6, and 7.1.7.2.7, respectively.

7.1.4 Eligibility Criteria

Prospective patients were required to meet the following inclusion and exclusion criteria in order to enroll in the study.

7.1.4.1 Key Inclusion Criteria

1) 18 years of age or older at the time of implantation.

2) 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

3) CNC word recognition score (mean of two lists) between 10% and 60%, inclusive (i.e., 10% $\leq$ score $\leq$ 60%), in the ear to be implanted

4) CNC word recognition score in the contralateral ear equal to, or better than, the ear to be implanted but not more than 80%

5) English spoken as a primary language

7.1.4.2 Key Exclusion Criteria

1) Duration of severe-to-profound hearing loss greater than 30 years

2) Congenital hearing loss (for the purpose of this study, onset prior to 2 years of age)

3) Medical or psychological conditions that contraindicate undergoing surgery

4) Ossification or any other cochlear anomaly that might prevent complete insertion of the electrode array

5) Conductive overlay of 15 dB or greater at two or more frequencies, from 250 to 1000 Hz

6) Hearing loss of neural or central origin

7) Diagnosis of Auditory Neuropathy

8) Active middle-ear infection.

9) 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

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

7.1.4.3 Surgical Procedure

In general, the following surgical steps for implantation of the Hybrid L24 are similar to all currently approved cochlear implants: creation of a sub-periosteal pocket and drilling of a well for the receiver stimulator, drilling an adequate mastoid cavity, creating a channel

to connect the well and the mastoid cavity, and drilling a facial recess approach to identify a round window niche. In the pivotal IDE study (G070191) for the Hybrid L24, only cochleostomy was specified and used to insert the electrode. In contrast, in the European clinical study of 66 subjects, only two subjects were implanted via cochleostomy and the remaining 64 via round window insertion. However, the applicant's surgical guide for the Hybrid L24 (Panel Packet, CI24REH surgeon's guide, page 11) states that the implantation can be accomplished either via round window or cochleostomy.

Reviewer Comment: *Note that the round window surgical approach was not used in the pivotal IDE but was used in 64 of 66 subjects in the European clinical study. The panel will be asked to comment on whether the current data support labeling for the round window surgical insertion technique.*

7.1.5 Statistical Analysis Plan

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

The primary safety endpoint was planned to be reported as the number and proportion of individuals experiencing an adverse event. Time to first adverse event (including total loss of residual hearing) was proposed to be summarized using Kaplan Meier plots. Audiometric data are summarized at each follow-up time point to assess any changes in hearing sensitivity and to characterize the impact of the procedure on residual low-frequency hearing.

Both the co-primary effectiveness endpoints were required to be met for study success. The null and alternative hypotheses for each of the co-primary endpoint are listed as follows:

> H_0: Mean improvement in primary effectiveness measure from baseline to 6 months post-implant (in Hybrid condition) ≤ 0.
>
> H_A: Mean improvement in primary effectiveness measure from baseline to 6 months post-implant (in Hybrid condition) > 0.

The 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.

For primary analyses, missing 6-month postactivation data were proposed to be imputed using the last observation carried forward (LOCF) approach. Sensitivity analyses were

performed to assess the robustness of results to different assumptions underlying the missing data. For the co-primary endpoints, both best-case and worst-case analyses were performed.

No formal hypothesis test was planned /conducted for the secondary endpoints or other effectiveness measures. Only descriptive statistics are presented.

7.1.6 Schedule of Study Visits

Candidacy testing included medical and audiological evaluations to determine study eligibility. A 2-week hearing aid trial was required for those prospective subjects who did not use hearing aids 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. The device was activated following a healing period of 2 to 4 weeks. Post-activation assessment sessions took place at the 3-, 6-, and 12-month intervals.

A summary of assessments performed as part of the pivotal study is provided in Table 2. The subject was informed that the study involves several visits (up to nine times) before and after surgery, for about a one year period. After one year, semi-annual visits were required through 3 years until the study closure (study not closed as of May 30, 2013). During each visit, device programming and all study assessments under study were completed during a 2-day period.

7.1.7 Assessments and Audiological Test Methods

7.1.7.1 Safety Test Methods

7.1.7.1.1 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 as 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 audiometric thresholds were obtained pre-operatively, and postoperatively upon device activation and at the 3-, 6-, and 12-month intervals.

7.1.7.1.2 Adverse Events

Adverse events were to be reported to the applicant via the adverse effects form provided to each center. The adverse effect form was filled out at each interval, and the centers were required to report adverse effects as soon as they were known. If the adverse effect

was reported by means other than the form, it was requested that the reporting party also complete the form and return to the applicant. A listing of the anticipated adverse effects follows:

1. Sudden changes in residual low-frequency hearing
2. Profound/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 states that since this study involved implanting subjects with residual low-frequency hearing sensitivity, for the purposes of adverse event reporting, any change in hearing that resulted in a profound (> 90 dB HL) or total (no measurable hearing) loss of low-frequency hearing (averaged over the range 125 through 1000 Hz inclusively) in the implanted ear was considered an anticipated adverse event and included in the adverse event tabulations and analyses.

7.1.7.2 Effectiveness Measures

7.1.7.2.1 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. This test was performed pre-operatively and postoperatively at the 3-, 6-, and 12-month intervals.

7.1.7.2.2 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. This test was performed pre-operatively and postoperatively at the 3-, 6-, and 12-month intervals.

7.1.7.2.3 Speech Reception Threshold (SRT) in Noise Test

The SRT in Noise Test is a single interval, 12-item forced-choice test, in which one of 12 target spondee words spoken by a female speaker is to be identified by the listener. This test was measured in an adaptive paradigm to determine the signal-to-noise ratio (SNR) for 50% correct. The test stimuli was presented with target stimuli at 60 dBA from 0° azimuth (frontal) in a background of broadband noise or two competing talkers presented at +/- 90° azimuth (loudspeaker to the right or left). The SRT in Noise Test was administered in two conditions: contralaterally to the ear to be implanted and bilaterally. This test was performed pre-operatively and postoperatively at the 6-month interval.

7.1.7.2.4 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. This test battery consists of 3 subtests each designed to provide an assessment of fundamental auditory skills important for music perception. One subtest provides an assessment of pitch perception, the second provides an assessment of melody recognition and the third subtest assesses the perception of timbre. The UW-CAMP was presented at 65 dBA in the following test conditions: unilaterally for the implanted ear and bilaterally. This test battery was performed postoperatively at the 6-month interval.

7.1.7.2.5 Speech, Spatial, and Sound Qualities Questionnaire (SSQ)

This questionnaire (Noble & Gatehouse, 2004), a patient-reported assessment of hearing in everyday life, is a tool that has undergone some degree of psychometric evaluation. It was adopted to assess subjects' hearing in everyday life across three categories, i.e., speech hearing rating scale, spatial rating scale, and sound qualities rating scale. This questionnaire was administered pre-operatively and postoperatively at the 6- and 12-month intervals.

7.1.7.2.6 Device Use Questionnaire (DUQ)

This in-house questionnaire was developed by the applicant to assess device usability and is not validated. It was administered to determine subjective preferences and satisfaction with regards to device use in various listening environments. This questionnaire was administered pre-operatively and postoperatively at the 6- and 12-month intervals.

7.1.7.2.7 Musical Background Questionnaire (MBQ)

This questionnaire (Gfeller et al., 2000) is a patient-reported questionnaire that has undergone some psychometric evaluation. It was adopted to examine listening habits with hearing aids, satisfaction with hearing aids for music listening, quality of music with hearing aids, enjoyment of musical styles with hearing aids, enjoyment of different instrumental timbres with hearing aids. This questionnaire was administered at the 6- and 12-month intervals.

The proposed test conditions for the effectiveness measures are defined in Table 1.

***Reviewer Comments**: The SSQ, DUQ and the MBQ are patient reported outcome measures. Since the initiation of the study in 2007, the Patient Reported Outcome Measures Labeling guidance was finalized in 2009. The Patient Reported Outcome Measures Labeling guidance (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm193282.pdf) describes how the FDA reviews and evaluates existing, modified or newly created patient-reported outcome instruments used to support claims. The instruments used in this study have undergone differing levels of psychometric evaluation; however, the information submitted does not completely substantiate the content or the construct validity of the patient reported questionnaires.*

7.2 Subject Accountability

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 [redacted],
        - 3 were no longer interested in pursuing a surgical procedure ([redacted] or had concerns regarding loss of residual hearing ([redacted],
        - 2 pursued traditional cochlear implantation ([redacted],
    - 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.

Of the 50 subjects who were enrolled and implanted, all had their device activated and reached the 3-month postactivation test interval. One subject ([redacted]) 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. One subject [redacted] completed speech perception testing but did not complete an audiometric evaluation. As a result, the number of subjects at the 6-month evaluation is 49 for effectiveness measures and 48 for the hearing sensitivity data. Of the 49 subjects,

- 46 completed the 12-month evaluation.
- Three subjects did not complete the 12-month evaluation: Two subjects withdrew prior to reaching the 12-month interval, one after being diagnosed with pancreatic cancer ([redacted], and the other due to advancing dementia ([redacted]. One subject [redacted]) was explanted and reimplanted with a Nucleus Freedom cochlear implant prior to the 12-month interval.

Reviewer Comment: *There were reasonable explanations for the minimal amount of missing data from the 6- and 12-month evaluations. Of note, three of the 100 consented subjects ([redacted]) chose not to proceed with implantation following a hearing-aid trial. Given the high incidence of profound or total loss of residual low-frequency hearing in a substantial proportion (22/50 subjects, 44 %) as of May 30, 2013, the panelists will be asked to comment on the appropriateness of requiring a hearing aid trial with properly fit hearing aids in the Indications for Use as a candidacy criterion for the device. If so, the panelists will also be asked to comment on the minimum length of such a hearing aid trial prior to candidacy.*

7.3 Demographics

Among the 50 implanted subjects, 25 were female and 25 were male. 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.

Table 3 summarizes descriptive statistics for the following variables: age at implantation, duration of hearing loss of any degree, duration of severe-to-profound high-frequency hearing loss, baseline CNC scores, and preoperative hearing loss in the low frequencies.

Further examination of the subjects' baseline covariates reveals that age at implantation, duration of hearing loss, and gender are correlated. Also, two variables, age at implantation and duration of hearing loss are positively correlated, as shown in Figure 6. Figure 7 displays histograms for the distribution of age at implantation by gender. Generally, male subjects were older than female subjects.

Baseline CNC scores and hearing thresholds were negatively correlated as expected. These two baseline variables are not found to be correlated with any of the other baseline variables listed in Table 3.

7.4 Protocol Deviations

Protocol deviations are instances where the investigational protocol was not followed. The applicant reports 50 protocol deviations during the study period, occurring in 29 subjects across nine of the 10 study sites. Table 4 provides a summary of the deviation type at each test interval, along with the number of deviations for each type listed.

Reviewer Comment: *The applicant provides a list of 50 protocol deviations (via an email dated 9/13/2013), each accompanied by a reason for deviation as well as justification for the lack of impact on determining safety and effectiveness outcomes of this study. FDA's review of these reported protocol deviations reveals no particular concerns about their impact on the safety endpoint and primary and secondary effectiveness endpoints.*

8. Pivotal Clinical Study Results

8.1 Safety Results

8.1.1 Unanticipated Adverse Events

The applicant reports there were no unanticipated adverse events (per 5.9.8 of submission Volumes 22-23).

8.1.2 Anticipated Adverse Events

Many of the anticipated adverse events (defined in 7.1.7.1.2) occurred during the study and were reported. Table 5 (submitted by the applicant) lists the types of anticipated adverse events, together with the number reported for each type, and the resolution status as of May 30, 2013. A summary of the adverse events follows:

- 34 subjects experienced 65 adverse events during the study.
    - Fifty (50) of the 65 events were reported as medical/surgical and the remaining 15 device related.
- Four subjects [redacted], and [redacted]) were explanted and reimplanted with currently approved standard length devices (either with CI24RE or CI512).
- Twenty-two (22) events in the corresponding 22 of 50 subjects (44%) were cases of post-operative profound or total loss of low-frequency hearing.
- 11 of 50 subjects (22%) experienced open and/or short circuits; these are reported by the applicant as resolved (Table 5).

The greatest number of adverse events reported was for profound or total hearing loss of low-frequency hearing (in 22 of 50 subjects). This issue is discussed in the reviewer comment below.

The applicant provides an analysis of time to first adverse event using the Kaplan-Meier plots. The Kaplan-Meier plots (Figure 8) were generated separately for all adverse events observed, adverse events related to profound/total loss of hearing, and for non-hearing related events. The applicant concludes that the adverse events observed during the study tended to occur within the first 6 to 8 months of device use postoperatively.

Reviewer Comment: *The most prevalent and significant adverse event of the study has been the loss of residual hearing up to profound or worse level experienced by 22 of 50 subjects (44%) of the study population as of May 30, 2013. The panel will be asked to comment on the safety profile of this device given the observed low-frequency residual hearing loss data.*

The second most prevalent adverse event was open and / or short circuit electrodes. Twenty-two percent (11 events out of 50 subjects) were reported for the Hybrid L24 trial which greatly exceeds the 4% (3/71) reported for the Freedom traditional cochlear implant clinical trial. However, the applicant states that in the Freedom cochlear implant trial all electrode shorts and opens were not reported. Therefore, the comparison of short/open electrodes between the two studies may be limited.

Regarding the analysis of adverse events using the Kaplan-Meier plots, it is important to note that hearing loss as analyzed is limited to the range of profound/total loss. Furthermore, the observation period is limited to the first 12 months. This analysis does not capture any of the profound/total loss in the four subjects whose loss was reported after the 12 month postoperative endpoint.

In Figure 9, the preoperative unaided air conduction thresholds for the implanted ear are shown with the shaded region representing the range of audiometric profiles fitting the selection criterion for the study. Subjects typically presented with normal through moderate levels of hearing loss up to 750 Hz and sloping to severe or profound high-frequency hearing loss.

Post-operatively, 48 subjects completed audiometric assessments at the 6-month interval, and the remaining two subjects were not assessed (both developed profound/total loss, and one was explanted/reimplanted). The proportion of subjects' changes in low-frequency hearing from pre- to postoperatively, at the 6- and 12-month intervals, are summarized in terms of the amount of loss (Table 6) and the degree of residual low-frequency hearing sensitivity (Table 7).

As of May 30, 2013 (not just at the endpoint of 6 months), 30 of 50 subjects experienced more than 30 dB loss in their residual low-frequency hearing. Five of these subjects' hearing sensitivity improved such that the amounts of low-frequency loss were within 30 dB of preoperative levels ([redacted] and [redacted] as of the most recent evaluation for each subject. Regarding the degree of residual low-frequency hearing sensitivity, as of May 30, 2013 (not just at the endpoint of 6 months), 22 of 50 subjects' residual low-frequency was at either the profound or total loss levels.

Reviewer Comment: *Of all subjects who experienced a "sudden change in residual hearing" (the first anticipated adverse event listed in 7.1.7.1.2), the applicant reports mainly on the subset of such subjects whose hearing sensitivity was at either profound or total hearing loss levels. While this is informative, please note there are some subjects who also lost hearing even though their loss was less than 30 dB and/or did not fall into the profound/total range (illustrated in Table 6 and Table 7 respectively). The panel will be asked to discuss the clinical significance of the residual low-frequency hearing loss > 10 dB but $\leq$ 30 dB experienced by 15 of 50 of the subjects at 6 months.*

8.1.3 Explantation/Re-implantation

Four of fifty subjects [redacted] and [redacted] underwent explantation of the original Hybrid L24 Implant due to the adverse event of profound to total loss of low-frequency hearing in their implanted ear at various time points post-operatively. Each of the four subjects were reimplanted with a traditional cochlear implant. Details surrounding explantation and reimplantation are summarized in Table 8.

8.2 Effectiveness Results

8.2.1 Primary Endpoints

Among the 50 subjects, 49 completed the testing for the co-primary endpoints at the 6-month interval. As discussed earlier in Section 7.2, one subject [redacted] did not complete testing at 6 months after seeking reimplantation with a traditional cochlear implant. However, this subject did complete the 3-month evaluation and had data available. The applicant conducted 4 types of analyses based on the following approaches: (i) analysis without imputation, (ii) imputation with a last observation carried forward (LOCF) approach, (iii) imputation using the worst-case, and (iv) imputation with the best-case for both co-primary endpoints. Table 9 summarizes the statistics for the scores at preoperative evaluation and 6-month interval, the change in scores between the two intervals, and the *p* values based on the Wilcoxon signed-rank test. The results indicate a significant improvement for both co-primary endpoints regardless of the analysis approach.

8.2.2 Secondary Endpoints

The secondary endpoint analyses were performed based on binomial comparisons of the scores for the CNC word recognition test, in terms of word and phoneme accuracy, and for the AzBio sentences-in-noise test between the Hybrid condition at the 6-month interval and the preoperative, ipsilateral Acoustic Alone (with a hearing aid) condition. The applicant's objective was to show that, for these secondary endpoints, the majority (> 75%) of the subjects scored equal to or better than they did in the preoperative ipsilateral Acoustic Alone condition.

Table 10 displays the proportion of subjects who performed poorer, equal, and better in the Hybrid condition for each secondary endpoint at the 6-month interval, when compared to the ipsilateral Acoustic Alone condition. The results indicate that over 75% of the subjects exhibited equal or better performance for all three endpoints. Regardless, there are 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 when compared to the preoperative performance.

Reviewer Comment: *The applicant presents these proportions based on 49 subjects who completed the 6-month evaluation in the PMA. However, this approach results in an*

overestimation of the proportion of subjects who scored equal to or better, since the subject ([redacted] excluded from the analysis had poor performance at the 3-month interval, and was subsequently re-implanted with a traditional cochlear implant between the 3- and 6-month intervals due to the limited benefits related to this subject's total loss of residual low-frequency hearing. The data for this subject collected at the 3-month interval revealed the following: the AzBio score decreased to 1.4% from 9.7% at preoperative baseline; the CNC word score decreased to 3% from 27% preoperatively; the CNC phonemes score decreased to 18.3% from 51.7% preoperatively. When this subject's data at 6 months were imputed using LOCF, the proportions who performed poorer are as reflected in the above text: 4% (as opposed to 2% without imputation) for CNC word accuracy, 10% (as opposed to 8.2%) for CNC phoneme accuracy,, and 12% (as opposed to 10.2%) for AzBio score.

Although not prospectively defined in their protocol, the applicant also analyzed their secondary endpoints in the Combined condition at 6 months versus in the baseline Bilateral Acoustic condition (i.e., with two hearing aids). Table 11 displays the proportion of subjects with the scores in the Combined condition at the 6-month interval equal or better than their preoperative performance in the Bilateral Acoustic condition. All subjects' scores were equal to or better than their preoperative performance, for all three secondary endpoints.

Reviewer Comment: *In the Hybrid condition, a small portion of study subjects performed poorer for CNC Words (4.0%), CNC Phonemes (10.0%), and the AzBio Sentences in Noise (12.0%), as compared to their pre-operative performance. In the Combined test condition, where the subjects used their contralateral residual low-frequency hearing, all subjects performed equal or better on these assessments. The panelists will be asked to discuss the clinical significance of these findings, and whether the Hybrid L24 should be explicitly indicated for unilateral implantation to preclude the possibility of residual low-frequency hearing loss in the contralateral ear.*

8.2.3 Effects of Baseline Characteristics on Device effectiveness

The applicant examined the consistency of primary endpoints across subgroups of subjects defined by the baseline characteristics: gender, age, duration of hearing loss, duration of severe to profound high-frequency hearing loss, etiology, and baseline speech perception scores. Grouping was performed based on dichotomous segregation for each variable (based on the median values for each variable), rather than covariate analyses. The FDA performed a covariate analysis. The analysis was based on all 50 subjects. The 6-month data of subject [redacted] who was explanted and received a traditional implant before 6 months, were imputed with the 3-month data.

Table 12 displays results based on the simple regression analysis. Each of the co-primary effectiveness endpoint variables (improvements in CNC and AzBio scores) was regressed on each of the baseline covariates, which include gender, age at implantation, duration of hearing loss, duration of severe to profound high-frequency hearing loss, baseline CNC scores, and pre-operative hearing threshold. Given that many of the baseline covariates

were correlated, multivariate regression analyses were further performed for CNC and AzBio. All of the six baseline variables were included in the multivariate regression model. The results in Table 13 indicate that device effectiveness, as determined by the scores of CNC Words and AzBio Sentences at the 6-month interval, is related to subjects' duration of hearing loss and pre-implant low-frequency hearing thresholds. Specifically, the mean CNC and AzBio scores were lower at the 6-month interval with longer durations of hearing loss and/or poorer baseline low-frequency hearing thresholds. The mean CNC scores were also lower at the 6-month interval with higher baseline CNC scores.

Reviewer Comments: *Two pre-implant baseline subject characteristics, pre-implant low-frequency hearing sensitivity and duration of hearing loss, are correlated with both co-primary effectiveness outcomes: improvements in CNC Word Recognition and AzBio Sentence-in-Noise tests at the 6-month interval.*

8.2.4 Site Effects

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 indicate no evidence of site effects on the primary effectiveness endpoints. The *p*-value is 0.42 for the CNC Words and 0.63 for the AzBio Sentences. Table 14 displays the summary statistics for CNC and AzBio results by site.

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

FDA conducted analysis to examine device effectiveness as a function of subjects' loss of residual low-frequency hearing, and the results are plotted in Figure 10 through Figure 13. All missing 6 month data were imputed with the corresponding 3-month data. Device effectiveness displayed in these figures is determined by the study co-primary endpoints, i.e., improvements in CNC words (Figure 10 and Figure 12) and AzBio sentences (Figure 11 and Figure 13), measured in the Hybrid condition. Subjects' loss of residual low-frequency hearing is characterized by (i) the amount of low-frequency hearing loss at 6 months with respect to baseline, preoperative acoustic alone for the treated ear (Figure 10 and Figure 11) and (ii) the low-frequency hearing sensitivity at 6 months (Figure 12 and Figure 13). The Pearson's correlation coefficient and the associated *p*-value are also displayed in each figure. As shown in these figures, there is 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 at 6 months) (all *p*-values < .0005). That is, the smaller the amount of loss in residual low-frequency hearing, the better the device effectiveness. Similarly, the more the residual hearing at the 6-month interval (i.e., that is preserved), the better the device effectiveness.

FDA further examined the consistency of the co-primary endpoints based on individual subjects' amounts of low-frequency hearing loss and residual low-frequency hearing

preserved at the 6-month interval. In this analysis, the amounts of loss at the 6-month interval are divided into four non-overlapping ranges, using the cutoff values at 10, 20, and 30 dB. Similarly, the preserved low-frequency hearing sensitivity at the 6-month interval is divided into the following four categories: 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 greater than 90 dB HL (a profound/total loss). The results are displayed in Table 15 through Table 18. Of note, those subjects with poorer performance for both co-primary endpoints not only exhibited a greater than 30 dB loss of residual low-frequency hearing, but also exhibited very little preserved hearing sensitivity (i.e., poorer than 90 dB HL, a profound/total loss). Furthermore, among those subjects with a greater than 30 dB loss of residual low-frequency hearing (N = 23), 34.8% (N=8) did not improve in both the CNC Word Recognition Test and the AzBio Sentence-in-Noise Test (Table 19). Similarly, among those subjects with a greater than 90 dB loss of residual low-frequency hearing (i.e., a profound/total loss) (N = 17), 47.1% (N = 8) did not improve in both in both the CNC Word Recognition Test and the AzBio Sentence-in-Noise Test (Table 20).

8.2.6 Changes in Effectiveness Over Time

The applicant provides a description of the changes in subjects' performance for the CNC Words and AzBio Sentences over the 12-month study period. The results, based on 49 subjects who completed the 6-month speech recognition tests at each time interval**,** are displayed in Table 21.

The amounts of improvement are the highest from the pre-operative baseline to the 3-month interval (ranging from 20-33% in mean difference) across all tests (CNC Words, Phonemes, and AzBio Sentences) and listening conditions (ipsilateral or bilateral). Regarding the amounts of the post-operative improvement over time, the changes are only a few percentage points, and notably the subject numbers decreased from 50 (pre-operative and 3-month) to 49 (6-month), then to 46 (12-month). These results may suggest that effectiveness outcomes do not decline over the period of 12 months.

8.2.7 Additional Effectiveness Measures

The applicant includes test results for the following additional tests, i.e., SRT, UW-CAMP, SSQ, DUQ, and MBQ, which are briefly summarized below:

Speech Recognition Threshold (SRT) in Noise Test –The SRT in Noise results indicate that significant improvement from the preoperative measurements. More 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, data for this test were only collected from 35 subjects, of whom 30 had better levels of low-frequency hearing in the implanted ear.

The University of Washington Clinical Assessment of Music Perception (UW-CAMP) – The UW-CAMP music test battery was administrated to assess 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 bilaterally and ipsilaterally at the preoperative baseline and at 6 months. The mean, standard deviation, and number who completed the test are presented in Table 22 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.

Speech, Spatial, and Qualities of Sound Questionnaire (SSQ) – SSQ include 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 23. The results indicate that the SSQ scores improved at 6 month postoperatively from the preoperative baseline.

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% (7/49) reported being dissatisfied or very dissatisfied. There were a total of 15 subjects with profound or total loss of hearing completed the DUQ. Among these 15 subjects, 80% (12) reported being very dissatisfied or dissatisfied, 6% (1/15) reported being neutral, while 15% (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.

Reviewer Comments: *Results from the SRT in Noise Test indicate that those subjects (N = 35), most with some amounts of preserved low-frequency hearing, received SRT advantage benefit when acoustic hearing was available via the contralateral or implanted ear. The UW-CAMP scores do not show that the Hybrid L24 subjects' music perception performance changes between the preoperative and the postoperative 6-month endpoint in the Hybrid condition. However, it is important to note that not all subjects completed each test at the 6-month interval, particularly for the SRT in Noise Test (N = 35). 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 current data set.

Regarding the patient-reported questionnaires, the SSQ, DUQ, and MBQ, the results indicate overall improvement or no change in perceived benefits and satisfaction with the Hybrid L24 post-operatively than pre-operatively. It is, however, important to note that 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. Given the concerns with the validity of these questionnaires (as indicated above in the Reviewer Comments under 7.1.7.2), and with the study design itself, the data derived from these patient-reported questionnaires may not be adequate to support claims regarding improvement in musical appreciation, patient-perceived sound quality, and device usability.

9. Post approval study (PAS)

Note: The inclusion of a Post-Approval Study section in this summary should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA device. The presence of a post-approval study plan or commitment does not in any way alter the requirements for pre-market approval and a recommendation from the Panel on whether the risks outweigh the benefits. The premarket data must reach the threshold for providing reasonable assurance of safety and effectiveness before the device can be found approvable and any post-approval study could be considered. The issues noted below are FDA's comments regarding potential post-approval studies, for the Panel to include in the deliberations, should FDA find the device approvable based upon the clinical premarket data.

The FDA review team recommends that if the Hybrid L24 is approved, two post-approval studies (PAS) should be required as conditions of approval for this first-of-a-kind device to assess 1) the long-term performance of the device and 2) performance in a broader population of patients and physicians. Through review of the premarket data, FDA has identified the following postmarket concerns:

- Long-term data on device effectiveness
- Long-term data on device safety
- Device performance in real world setting.

The applicant submitted a PAS protocol for an extended follow-up of the premarket pivotal cohort study and a PAS protocol for a new enrollment study on September 6, 2013. An overview of the PAS proposals is provided below, followed by FDA's assessment.

A. OVERVIEW OF APPLICANT'S PAS PROPOSALS

The applicant is proposing to conduct two post-approval studies: (1) An extended follow-up of the premarket pivotal study cohort, and (2) A new enrollment study to evaluate real

world effectiveness and safety. The following tables present the applicant's PAS proposals.

1. **Extended Follow-up of the PMA Cohort:**

Study Component	**Description**
Study Objective	The purpose of the study is to conduct extended duration (5 years post-implant) monitoring of the safety and effectiveness of the Hybrid L24 Implant System.
Study Design	The study is a single arm study in which each patient serves as his or her own control.
Study Population	This study will be comprised of up to 47 patients who were implanted with the Hybrid L24 under the premarket pivotal study, and who will agree to participate in a further evaluation of an approved sound processor with new, investigational features. (Note: The applicant is currently investigating a new noise reduction and environmental classification features in the existing pivotal study cohort using the next generation CP900 processor under G070191 IDE (approved on July 17, 2013)).
Sample Size (Patients and Sites)	Up to 47 patients enrolled in the premarket pivotal study (at 10 U.S. investigational centers).
Endpoints	The primary safety endpoint will be the comparison of the type and frequency of adverse events (and serious adverse events) occurring over the course of this study (up to 60 months) as compared to the pivotal clinical study for the Hybrid L24. The co-primary efficacy endpoints for this study will be the assessment of statistical significance of the within-subject differences for two speech recognition tests: • **Word recognition in quiet as evaluated with the Consonant-Nucleus-Consonant (CNC) test** • **Sentence recognition in noise (+10dB) as evaluated with the AzBio test**
Follow-up Visits and Length of Follow-up	The following tests will be administered annually: • Otologic/medical questionnaire (health history) • Unaided audiometric threshold measures for each ear • CNC Words presented in quiet at 60 dBA • AzBio sentences presented at 60 dBA with + 10dB SNR

	○ Each speech perception metric will be administered in the following two conditions: ▪ Unilateral Condition: Hybrid mode or CI alone if subject no longer utilizes the acoustic component. ▪ Everyday Listening Condition: Combined, Bimodal, Hybrid or CI alone • Modified device use questionnaire • Health Utility Index (HUI) Patients will be followed for 5 years after device activation.
Enrollment Plan and Follow-up Measures	Conservatively, it is anticipated that there could be a 30% lost-to-follow-up rate. Attempts will be made to enroll as many of the study eligible candidates (n=47) as possible. Study candidates will be approached in parallel to their enrollment into the new IDE study (G070191) which is designed to evaluate new sound processor features for the Hybrid L24 system. Study duration is not expected to exceed 36 months as all current Hybrid L24 study subjects will have been implanted at least two years by the time of PMA approval and PAS initiation and enrollment.
Statistical Plan	**Analysis of Safety** • Adverse Events and Serious Adverse Events will be expressed as events per patient–time. • All adverse event rates will be reported as the number and frequency of events with corresponding 95% exact binomial confidence limits and the number of events per patient-time (e.g., events per 10 patient years), and compared qualitatively to previous cochlear implant studies. • Time to first adverse event (including total losses of residual hearing) will be summarized using Kaplan Meier plots. Exploratory proportional hazards regression models will be used to determine whether baseline factors are associated with risk for adverse events over follow-up. Hazard ratios and 95% confidence intervals for these analyses will be cited. **Analysis of Efficacy** The significance of the mean differences in speech recognition scores between preoperative and the 60 months post-activation interval (study completion) will be analyzed using paired t- tests. If there was significant evidence that the assumptions of the t-tests did not hold (i.e. $p < 0.05$ from a Shapiro-Wilk test of normality), then Wilcoxon signed rank tests will be used.
Timeline for Study	Not provided.

Implementation	

2. **New Enrollment Study:**

Study Component	**Description**
Study Objective	The purpose of the study is to conduct long term monitoring (36 months) of the safety and effectiveness of the Hybrid L24 Implant System.
Study Design	This is a prospective, non-controlled, non-randomized and multicenter study.
Study Population	Patients will include a minimum of 50 individuals, 18 years of age and above, who have received the Hybrid L24. The study cohort will consist of newly implanted (post PMA approval) Hybrid L24 recipients.
Sample Size (Patients and Sites)	A minimum of 50 patients enrolled at up to 25 investigative centers.
Endpoints	The primary safety endpoint will be the comparison of the type and frequency of adverse events (and serious adverse events) occurring over the course of this study (36 months) as compared to the pivotal clinical study for the Hybrid L24. The co-primary efficacy endpoints for this study will be the assessment of statistical significance of the within-subject differences for two speech recognition tests: • **Word recognition in quiet as evaluated with the Consonant-Nucleus-Consonant (CNC) test** • **Sentence recognition in noise (+10dB) as evaluated with the AzBio test**
Follow-up Visits and Length of Follow-up	Data will be collected at baseline, initial device activation, 6-, 12-, 24- and 36 months post-activation, The following tests will be administered at post-activation and annual follow-ups: • Otologic/medical questionnaire (health history) • Unaided audiometric threshold measures for each ear • CNC Words presented in quiet at 60 dBA • AzBio sentences presented at 60 dBA with +10dB SNR o Each speech perception metric will be administered in the following two conditions:

	▪ Unilateral Condition: Hybrid mode or CI alone if subject no longer utilizes the acoustic component. ▪ Everyday Listening Condition: Combined, Bimodal, Hybrid or CI alone • Modified device use questionnaire • Health Utility Index (HUI) Patients will be followed for 3 years post-activation.
Enrollment Plan and Follow-up Measures	Conservatively, it is anticipated that there could be a 30% lost-to-follow-up rate. Therefore, recruitment will be sufficient to account for this potential attrition.
Statistical Plan	**Analysis of Safety** • Adverse Events and Serious Adverse Events will be expressed as events per patient-time. • All adverse event rates will be reported as the number and frequency of events with corresponding 95% exact binomial confidence limits and the number of events per patient-time (e.g., events per 10 patient years), and compared qualitatively to previous cochlear implant studies. • Time to first adverse event (including total losses of residual hearing) will be summarized using Kaplan Meier plots. Exploratory proportional hazards regression models will be used to determine whether baseline factors are associated with risk for adverse events over follow-up. Hazard ratios and 95% confidence intervals for these analyses will be cited. **Analysis of Efficacy** The significance of the mean differences in speech recognition scores between preoperative and the 36-months post-implant interval will be analyzed using paired t-tests. If there was significant evidence that the assumptions of the t-tests did not hold (i.e., $p < 0.05$ from a Shapiro-Wilk test of normality), then Wilcoxon signed rank tests will be used.
Timeline for Study Implementation	Not provided.

B. FDA ASSESSMENT OF THE PAS PROPOSALS

Extended Follow-up Study

The applicant has proposed to continue to follow 47 patients enrolled and implanted with the device in the premarket pivotal study for 5 years post-implantation. This is appropriate because the patients in the pivotal study completed their 12 month study visits; therefore, extended follow-up of the premarket cohort is necessary to assess the longer-term performance of the device.

The study population will include patients who were implanted with the Hybrid L24 (premarket pivotal study cohort) who have agreed to participate in a new evaluation of investigational features of CP900 series sound processor. The applicant investigates new noise reduction and environmental classification features in the existing pivotal cohort using the next generation CP900 processor under IDE G070191, approved on July 17, 2013. The CP900 series of sound processors has the ability to run these three new features: Signal-to-Noise Ratio – Noise Canceller (SNR-NC), Wind-Noise Reduction (WNR), and Environmental Classifier (EC). A summary of these features is provided in the Regulatory History section of this executive summary. The applicant proposes to study the premarket pivotal cohort for the investigational features of CP900 series sound processors as well as for the long-term safety and effectiveness of the Hybrid L24. However, the PAS protocol did not explain how the measurements will be conducted to evaluate the safety and effectiveness of the device. The FDA does not believe that there are any additional safety concerns associated with the use of the new, investigational features. There may be several factors with the new, investigational features that could impact the assessment of device effectiveness for the Hybrid L24. For example, if the patients will be using the device with the new features except for the time of measurements in the office visit, there could exist a potential carry-over effect when the features are turned off for the purpose of the study measurements. The sponsor did not provide information on how they plan to measure the effectiveness of the Hybrid L24 Implant System in patients who have agreed to have a modified device with new investigational features. The panel will be asked to discuss the appropriateness of the proposed study population to evaluate the long-term safety and effectiveness of the Hybrid L24 Implant System.

In addition, the sponsor has proposed that the device effectiveness will be assessed by comparing the mean differences in speech recognitions measured by CNC and AzBio tests between preoperative and 60 months post-activation interval. The panel will be asked to discuss how device effectiveness should be measured in this study considering the proposed study population.

New Enrollment Study

The applicant is proposing to conduct a study with a minimum of 50 newly enrolled patients at up to 25 clinical sites. This is appropriate because the premarket pivotal study conducted for this device included highly specialized physicians and highly selected patients. Therefore, there is a need for a study with newly enrolled patients with a broader physician

population in order to evaluate the safety and effectiveness of the device in the real-world setting.

The primary effectiveness endpoint is to assess within patient differences between pre-operative and the 36 months post-activation interval in the two speech recognition tests, i.e., Consonant-Nucleus-Consonant (CNC) test and AzBio test. The panel will be asked to discuss if there are any additional long term effectiveness endpoints that should be evaluated in the postmarket setting.

As part of annual follow-up evaluations, the applicant has proposed to collect data on patient reported outcomes by administering a modified device use questionnaire (DUQ) and health utility index (HUI) questionnaire. The DUQ is not a validated instrument, and the HUI is a generic instrument. The panel will be asked to discuss appropriate validated instruments that could be used in this study for the assessment of patient reported outcomes.

The applicant has proposed to follow the patients for 3 years after the device activation. However, the FDA recommends following the patients for 5 years since this is a first-of-a-kind device with a unique design change and expanded indication for use. The panel will be asked to discuss the appropriate duration of follow-up in order to assess the long term device performance.

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Tables

Table 1: Test Conditions (post implantation)

Condition	*Hybrid**	*Bimodal*	*Combined (Everyday use)*
Description	use of acoustic hearing (via amplification), in addition to electric hearing (via the Hybrid L24 implant in the same ear)	use of acoustic hearing, in addition to electric hearing in the opposite ear	use of acoustic hearing bilaterally, in addition to electric hearing (i.e., a combination of the Hybrid and Bimodal conditions)
			

* For those subjects who developed profound/total loss of residual low-frequency hearing, the applicant performed testing for the Hybrid L24 implant only (electric-alone mode) in place of the Hybrid condition but include these data in the Hybrid condition.
(Illustrations are adopted & modified from the applicant's submission, P130016, page 85, Volume 1.)

Table 2: 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*
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

*Aided thresholds were only retested if there was a change in unaided hearing sensitivity at that interval compared to the previous interval.

[1] Subjects continued to be monitored on a semi-annual basis after 12-month interval.
(Table included from the applicant's submission, Volume 1, p. 92 of 150)

Table 3: 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 score (%)	28.4	14.7	9	64
Preoperative low-frequency hearing sensitivity (from 125-1000 Hz, dB HL)	45.3	10.2	19	63

Table 4: Summary of protocol deviations

Test Interval	*Deviation Type*	*Number of Deviations*
Candidacy	Consent by non-authorized staff member	1
	Candidacy criteria not met	2
	Hearing aid trial not fulfilled	1
Baseline	hearing aid verification not completed	2
	Technical / examiner error	4
Intraoperative	Electrode impedance not assessed or saved	4
	Wrong ear implanted	2
Initial Activation	Acoustic component not fit or verified / hearing aid verification not completed	7
	Technical / examiner error	2
	Performed prior to 1- month post- surgery	1
	Measure not performed	3
3 months	Tests done outside of test-retest window	1
	Complete mapping data not collected	4
	Hearing aid verification not completed or recorded	2
6 months	Electrode impedance not assessed	2
	Tests* not performed or results not saved	6
	Technical / examiner error	1
	hearing aid verification not completed	2
12 months	Technical / examiner error	2
	Semiannual visits did not occur	1
		Total = 50

* These tests were not related to the primary endpoint measures.

Table 5: Anticipated adverse events

Adverse Event	Number Occurring	Number Resolved	Number Unresolved
Profound/Total loss of hearing	22	0	22
Increased Tinnitus	6	6	0
Tinnitus not present preoperatively	6	6	0
Increased tinnitus with change in hearing	2	2	0
Device Related (Opens/Shorts)	11	11	0
Dizziness	3	3	0
Dizziness with change in hearing	2	2	0
Imbalance	1	1	0
Imbalance with change in hearing	1	1	0
Vertigo	1	1	0
Vertigo with change in hearing	1	1	0
Sound Quality Issues	2	1	1
Decreased Performance	1	0	1
Increased impedances with change in hearing sensitivity	1	1	0
Overstimulation	1	1	0
Other*	4	4	0

- 'Other' includes 2 reports of transient skin irritation due to externals, 1 case of pain associated with middle ear effusion, and 1 case of a local stitch infection.

(Table provided by applicant on August 22, 2013)

Table 6: 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])*	*6-month (N = 48[2])*	*12-month (N = 46[3])*
≤ 10	24.0% (12/50)	25.0% (12/48)	19.9% (9/46)
≤ 20	48.0% (24/50)	50.0% (24/48)	45.7% (21/46)
≤ 30	54.0% (27/50)	56.3% (27/48)	58.7% (27/46)
> 30	46.0% (23/50)	43.8% (21/48)	41.3% (19/46)

[1] Data for the 6-month interval reported in this column are based on the data imputed using LOCF (N = 50). More specifically, data were imputed for two subjects: Subject [redacted] (loss of 42.4 dB at 3 months) was explanted and reimplanted with a Nucleus 5 cochlear implant before 6 months. Subject US14-1050 (loss of 63.6 dB at 3 months) did not complete the audiometric evaluation at 6 months; this subject was later explanted and reimplanted with a Nucleus Freedom cochlear implant.
[2] Results reported in this column are based on all available data obtained from the subjects evaluated at 6 months (N = 48). Data from Subject [redacted] and Subject [redacted] were not obtained and thus not included.
[3] Results reported in this column are based on the data obtained from the subjects evaluated at 12 months (N = 46). Two subjects, Subject [redacted] (loss of 75 dB at 6 months) and [redacted] (loss of 4 dB of at 6 months) withdrew from the study between 6 and 12 months.

Table 7: Proportion of subjects' low-frequency hearing sensitivity at 6 and 12 months

Residual low-frequency hearing sensitivity (dB HL)	*6-month (N = 50[1])*	*6-month (N = 48[2])*	*12-month (N = 46[3])*
41 – 55 (Moderate loss)	30.0% (15/50)	31.3% (15/48)	32.6% (15/46)
56 – 70 (Moderately severe loss)	18.0% (9/50)	18.8% (9/48)	21.7% (10/46)
71 – 90 (Severe loss)	18.0% (9/50)	18.8% (9/48)	17.4% (8/46)
> 90 (profound)	24.0% (12/50)	20.8% (10/48)	17.4% (8/46)
no measurable hearing (Total loss)	10.0% (5/50)	10.4% (5/48)	10.9% (5/46)

[1] Data for the 6-month interval reported in this column are based on the data imputed using LOCF (N = 50). More specifically, data were imputed for two subjects: Subject [redacted] (102.4 dB HL at 3 months) and Subject [redacted] (107.6 dB HL at 3 months). Please refer to Note 1 for Table 6 above for additional details about these subjects.
[2] Results reported in this column are based on all available data obtained from the subjects evaluated at 6 months (N = 48). Data from Subject [redacted] and Subject [redacted] were not obtained and thus not included.
[3] Results reported in this column are based on the data obtained from the subjects evaluated at 12 months (N = 46). Two subjects, Subject [redacted] (no measurable hearing, recorded as 132 dB HL at 6 months) and [redacted] (48 dB HL at 6 months) withdrew from the study between 6 and 12 months.

Table 8: Summary of Hybrid L24 explantation and reimplantation with traditional CI

Subject ID	Date of Hybrid Implant	Adverse Event	Date of Explant/Re-Implant	Reason for Explantation/ Reimplantation	Current Status
[redacted]	01/05/2011	Four months following implantation hearing progressed to profound/total hearing loss	6/29/2011 **Surgical Information:** Significant Fibrous growth in cochlea	Device issue (partial short circuit), hearing loss, and poor performance.	Using CI512
[redacted]	02/10/2011	Five months following implantation deteriorated to profound/total hearing loss	3/8/2012	Subject dissatisfied. Re-implanted to address hearing loss and poor performance at 12 months	Using CI24RE
[redacted]	02/26/2011	First change in hearing noted at 3 months and then progressed to profound/total hearing loss	2/6/2013	Subject dissatisfied. Reimplanted to address hearing loss and poor performance at 18 months	Using CI24RE
[redacted]	05/04/2011	Significant change in hearing identified at activation, progressed to profound/total hearing loss	07/18/2012	Subject dissatisfied. Reimplanted to address hearing loss and poor performance after 12 months	Using CI24RE

Table 9: Co-primary endpoint results based on four different analysis approaches: 49 completed case, LOCF imputation, worst case imputation, and best case imputation

Co-primary Endpoint	*N (Analysis Approach)*	*Acoustic Alone Preoperative Mean ± SD (%)*	*Hybrid Mode 6 Months Mean ± SD (%)*	*Change Mean ± SD (%)*	*(95% C.I.)*	*p-value*
CNC	49 (available)	28.4 ± 14.7	65.4 ± 25.4	37.0 ± 26.6	(29.4, 44.6)	< 0.0001
	50 (LOCF)	28.4 ± 14.7	64.2 ± 26.6	35.8 ± 27.7	(27.9, 43.8)	< 0.0001
	50 (worst case)	28.4 ± 14.7	64.1 ± 26.7	35.7 ± 27.8	(27.8, 43.6)	< 0.0001
	50 (best case)	28.4 ± 14.7	66.1 ± 25.6	37.7 ± 26.8	(30.1, 45.3)	< 0.0001
AzBio	49 (available)	16.3 ± 14.4	49.2 ± 30.8	32.8 ± 29.1	(24.5, 41.2)	< 0.0001
	50 (LOCF)	16.3 ± 14.4	48.3 ± 31.3	32.0 ± 29.4	(23.7, 40.4)	< 0.0001
	50 (worst case)	16.3 ± 14.4	48.3 ± 31.3	32.0 ± 29.4	(23.6, 40.4)	< 0.0001
	50 (best case)	16.3 ± 14.4	50.3 ± 31.4	34.0 ± 29.9	(25.5, 42.5)	< 0.0001

Table 10: Proportion of subjects who performed poorer, equal, or better in the Hybrid versus the (ipsilateral) Acoustic Alone condition at 6 months for each secondary endpoint

Endpoint	*Poorer*	*Equal*	*Better*
CNC Words	4.0% (2/50[1])	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)

[1] Data reported here are based on the data imputed using LOCF (N = 50). More specifically, data were imputed for [redacted] ('poorer' for all three secondary endpoints at 3 months). See Note 1 of Table 6 above for additional details about this subject.

Table 11: Proportion of subjects who performed poorer, equal, or better in the Combined versus the Bilateral Acoustic condition at 6 months for each secondary endpoint

Endpoint	*Poorer*	*Equal*	*Better*
CNC Words	0% (0/50[1])	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)

[1] Data reported here are based on the data imputed using LOCF (N = 50). More specifically, data were imputed for one subject, [redacted] ('better' for all three secondary endpoints at 3 months). Please refer to Note 1 for Table 6 above for additional details about this subject.

Table 12: Results from regression analysis for each co-primary effectiveness endpoint on each baseline subject characteristic

Subject characteristic	*Improvement in CNC scores*		*Improvement in AzBio scores*	
	Estimate	*p-value*	*Estimate*	*p-value*
Gender (female vs. male)	20.2	**0.009**	17.10	**0.038**
Age at implantation (years)	-0.80	**0.002**	-0.75	**0.007**
Duration of hearing loss (years)	-0.87	**<0.001**	-0.90	**<0.001**
Duration of severe hearing loss (years)	-0.43	0.439	-0.41	0.481
CNC Words (%)	-0.64	**0.016**	-0.06	0.826
Low-frequency hearing threshold (dB)	-0.38	0.332	-0.97	**0.017**

Table 13: 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)	-0.94	**0.023**	-1.08	**0.013**

Table 14: Number of subjects and group performance at each study site at 6 months

Site	*N*	*% Improvement in CNC mean ± SD*	*% Improvement in AzBio mean ± SD*
0029	6	54.2 ± 21.6	54.6 ± 36.3
1001	3	57.0 ± 19.1	45.5 ± 31.3
1003	10	35.6 ± 33.0	26.5 ± 31.7
1050	11	37.1 ± 17.0	26.7 ± 21.9
1059	3	21.3 ± 31.6	20.8 ± 37.0
1131	7	22.6 ± 36.8	32.6 ± 29.7
1168	3	42.7 ± 23.0	42.9 ± 24.0
1339	3	48.7 ± 7.5	36.1 ± 29.9
1411	1	19.0	–3.8
1523	2[1]	19.0 ± 15.6	31.6 ± 33.2
	p-value	0.42	0.63

[1] Data were available for only 2 of 3 subjects at this site.

Table 15: Proportion of subjects who performed poorer, equal, or better for the CNC Word Recognition Test in the Hybrid versus the Acoustic Alone condition at 6 months, as a function of the amount of change in low-frequency hearing

Amount of change in low-frequency hearing (dB)	*Mean (STD) (%)*	*Proportion of subjects*			
		Poorer	*Equal*	*Better*	*Total*
≤ 10	56.5 (21.2)	0% (0/50)	**2% (1/50)**	22% (11/50)	24% (12/50)
> 10, ≤ 20	41.9 (18.2)	0% (0/50)	0% (0/50)	24% (12/50)	24% (12/50)
> 20, ≤ 30	40.3 (10.0)	0% (0/50)	0% (0/50)	6% (3/50)	6% (3/50)
> 30	21.2 (28.9)	**4% (2/50)**	**14% (7/50)**	28% (14/50)	46% (23/50)

Table 16: Proportion of subjects who performed poorer, equal, or better for the AzBio Sentence-in-Noise Test in the Hybrid versus the Acoustic Alone condition at 6 months, as a function of the amount of change in low-frequency hearing

Amount of changes in low-frequency hearing (dB)	*Mean (STD) (%)*	*Proportion of subjects*			
		Poorer	*Equal*	*Better*	*Total*
≤ 10	55.6 (23.7)	0% (0/50)	**2% (1/50)**	22% (11/50)	24% (12/50)
> 10, ≤ 20	34.3 (20.4)	0% (0/50)	0% (0/50)	24% (12/50)	24% (12/50)
> 20, ≤ 30	29.9 (29.6)	0% (0/50)	**2% (1/50)**	4% (2/50)	6% (3/50)
> 30	18.8 (29.4)	**12% (6/50)**	**12% (6/50)**	22% (11/50)	46% (23/50)

Table 17: Proportion of subjects who performed poorer, equal, 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	*Equal*	*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 18. Proportion of subjects who performed poorer, equal, 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	*Equal*	*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)

Table 19: Proportion of subjects with a greater than 30 dB loss of residual low-frequency hearing, with poorer, equal, or better for CNC Word Recognition scores and AzBio Sentence-in-Noise scores in the Hybrid condition

AzBio / *CNC*	*Poorer*	*Equal*	*Better*	*Total*
Poorer	**8.7% (2/23)**	0% (0/23)	0% (0/23)	8.7% (2/23)
Equal	**13.0% (3/23)**	**13.0% (3/23)**	4.3% (1/23)	30.4% (7/23)
Better	4.3% (1/23)	13.0% (3/23)	43.48% (10/23)	60.9% (14/23)
Total	26.1% (6/23)	26.1% (6/23)	47.8% (11/23)	100% (23/23)

Table 20: Proportion of subjects with greater than 90 dB of residual low-frequency hearing sensitivity, with poorer, equal, or better for CNC Word Recognition scores and AzBio Sentence-in-Noise scores in the Hybrid condition

AzBio / *CNC*	*Poorer*	*Equal*	*Better*	*Total*
Poorer	**11.8% (2/17)**	0% (0/17)	0% (0/17)	11.8% (2/17)
Equal	**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)

Table 21: Group mean CNC Words, CNC Phonemes, and AzBio scores over time

Test Interval	*Pre-operative (N = 50)*	*3-month (N = 50)*	*6-month (N = 49)*	*12-month (N = 46)*
CNC Words (I)	28.4%	58.5%	65.4%	69.4%
CNC Words (B)	44.9%	75.9%	79.4%	82.0%
CNC Phonemes (I)	51.4%	73.0%	78.3%	81.5%
CNC Phonemes (B)	67.6%	87.7%	89.8%	91.1%
AzBio Sentences (I)	16.3%	44.6%	49.2%	51.5%
AzBio Sentences (B)	29.6%	62.6%	62.6%	66.3%

I: Ipsilateral – hearing aid in the implanted ear (pre-operative) or Hybrid L24 including the acoustic component (3-, 6-, and 12-months)
B: Bilateral – bilateral hearing aids (pre-operative) or Hybrid L24 including the acoustic component and contralateral acoustic hearing aid (3-, 6-, and 12-months)

Table 22: Descriptive statistics (Mean ± Standard Deviation)) for UW-CAMP: pitch discrimination in semitones, melody and timber identification in percent correct

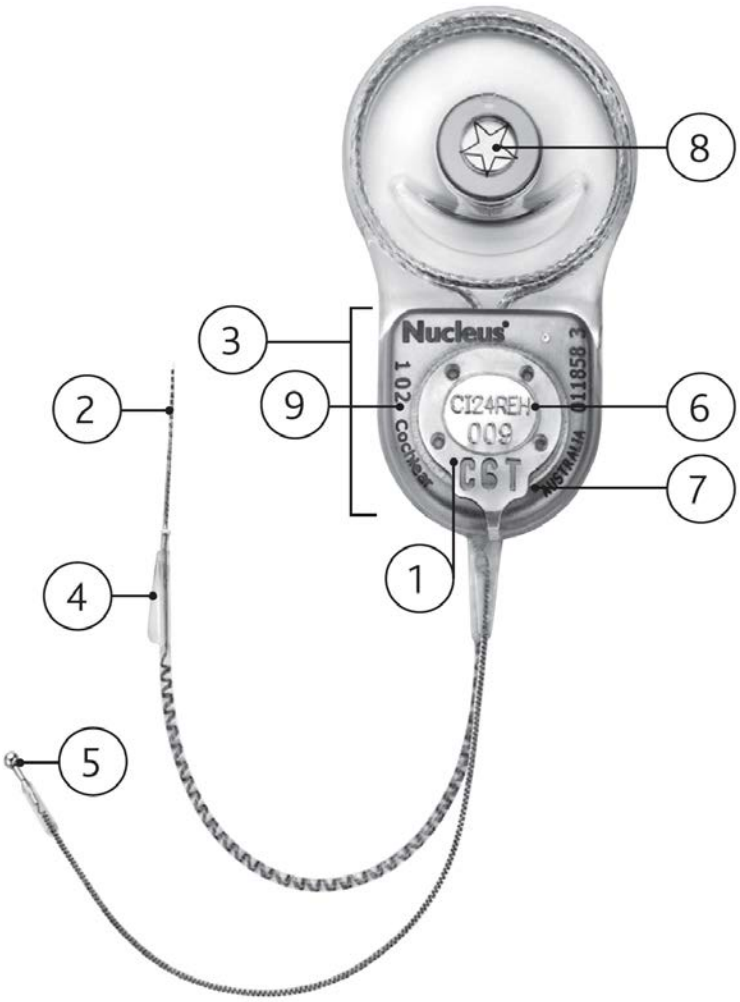
Subtest	*Ipsilateral (implanted ear alone)*		*Bilateral (both ears)*	
	Acoustic at baseline	*Hybrid at 6 months*	*Bilateral at baseline*	*Combined at 6 months*
Pitch (semitone)	1.1 ± 1.0 (N = 50)	1.4 ± 1.5 (N = 46)	1.1 ± 1.1 (N = 50)	1.0 ± 0.8 (N = 46)
Melody (% correct)	66.2 ± 25.7 (N = 50)	65.9 ± 29.5 (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)

Table 23: 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

Figures

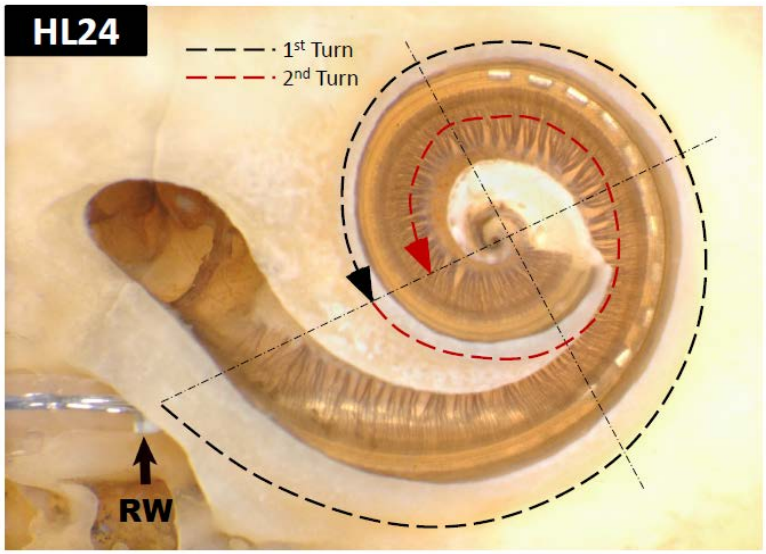
Figure 1: Hybrid L24 implant (CI24REH with Hybrid L24 array)



1. Receiver/stimulator
2. Intracochlear electrode array
3. Extracochlear electrode (plate)
4. Handle
5. Extracochlear electrode (ball)
6. Model (CI24REH)
7. Radiopaque characters [Manufacturer (C = Cochlear), Model (6 = Hybrid L24), Year made (T = 2004 and later)]
8. Magnet (star on skin side)
9. Serial number

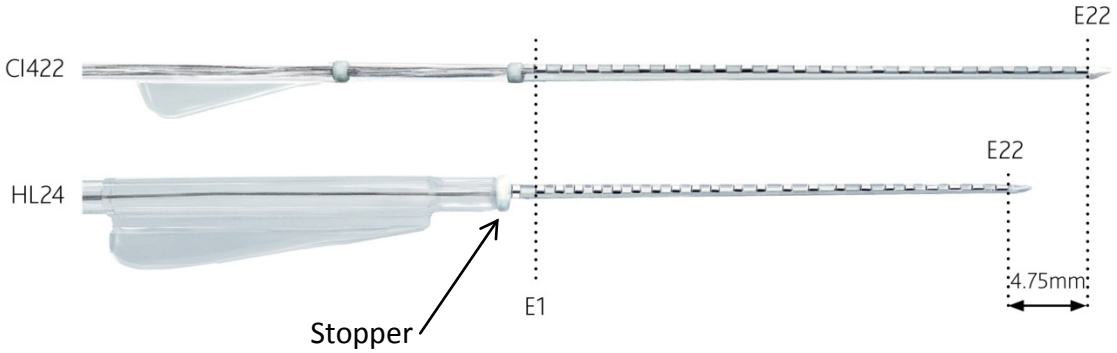
(Figure provided by the applicant on September 5, 2013)

Figure 2: Image of Hybrid L24 array inserted in cochlea



(Figure provided by the applicant on July 26, 2013)

Figure 3: Comparison of approved CI422 array (top) and Hybrid L24 array (bottom)

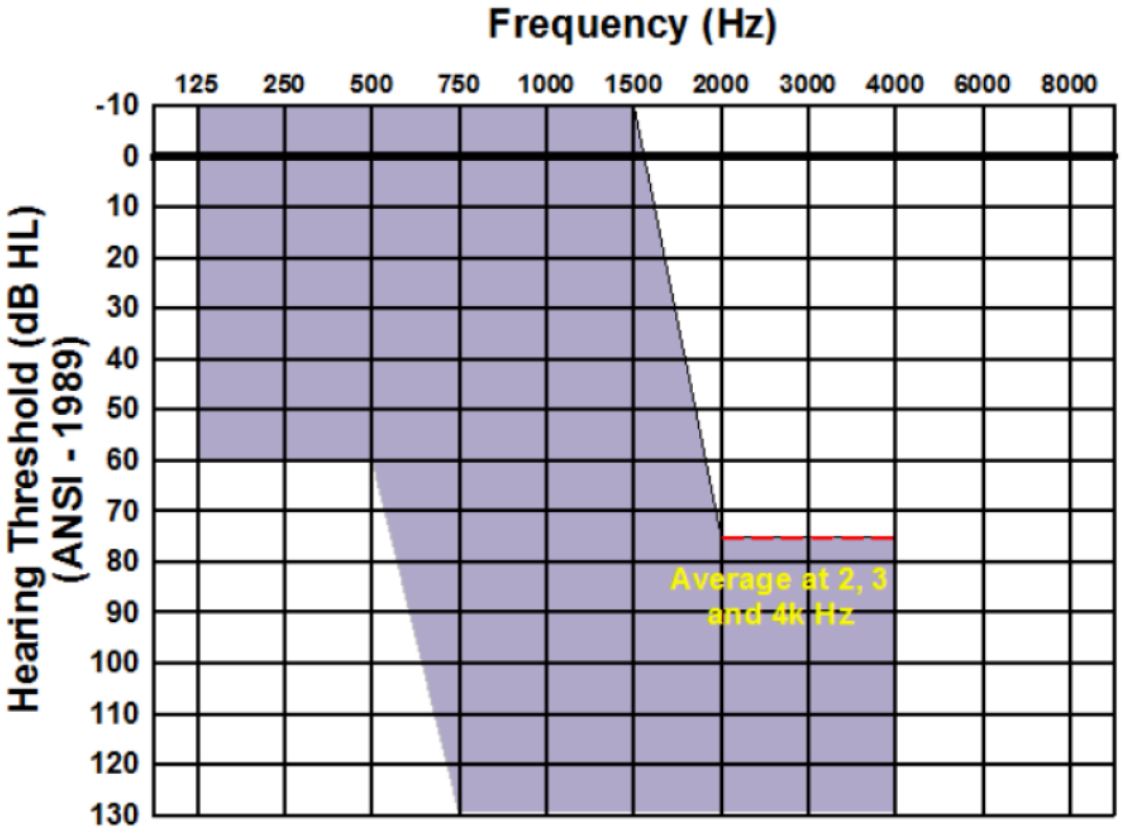


(Figure annotated from that provided by applicant on September 16, 2013)

Figure 4: Top panel: CP920 (left) and CP910 (right) sound processors. The CP910 includes an audio accessory port, otherwise, the two processors are identical. Bottom panel: Acoustic Component shown with CP910.

(Figures included from applicant's submission, Vol. 1, page 13)

Figure 5: Audiogram range for subjects included in the pivotal study



(Figure included from applicant's submission, Vol. 1, Tab 5, page 16),

Figure 6: Relationship between duration of hearing loss and age at implantation

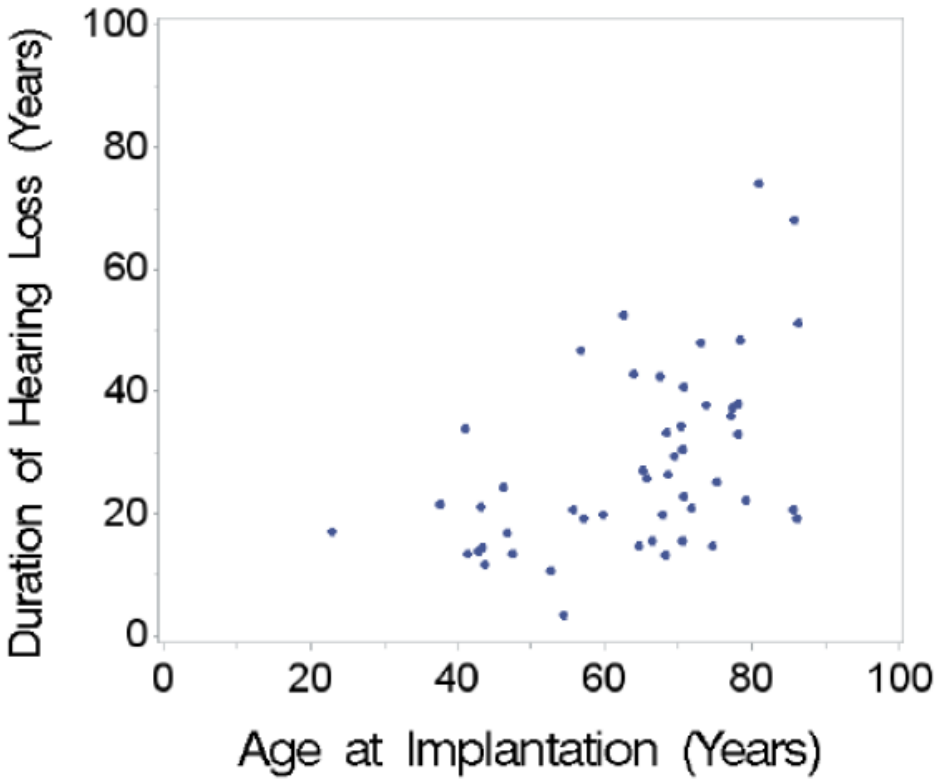


Figure 7: Histograms for the distribution of age at implantation by gender

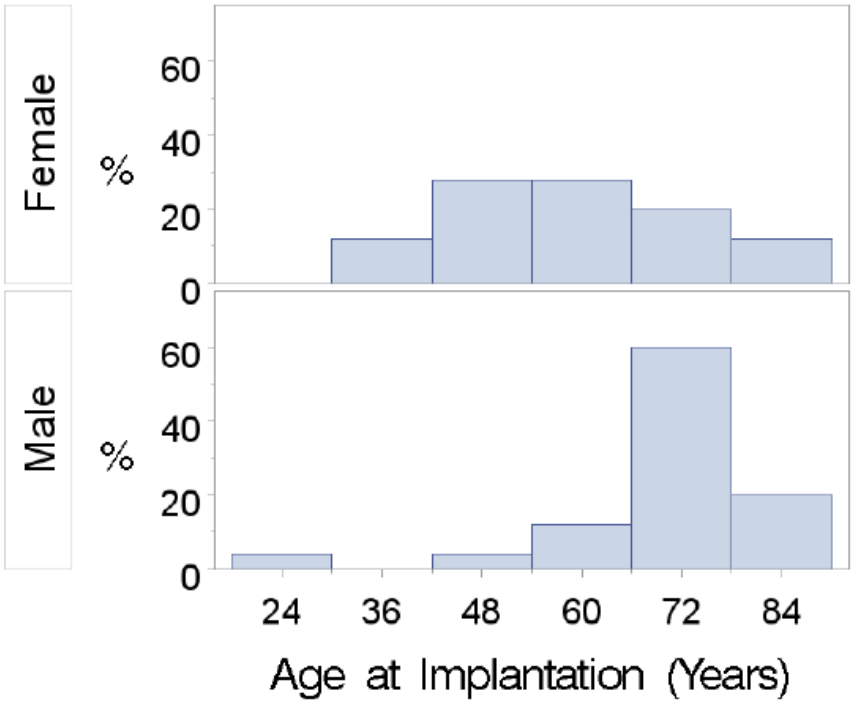
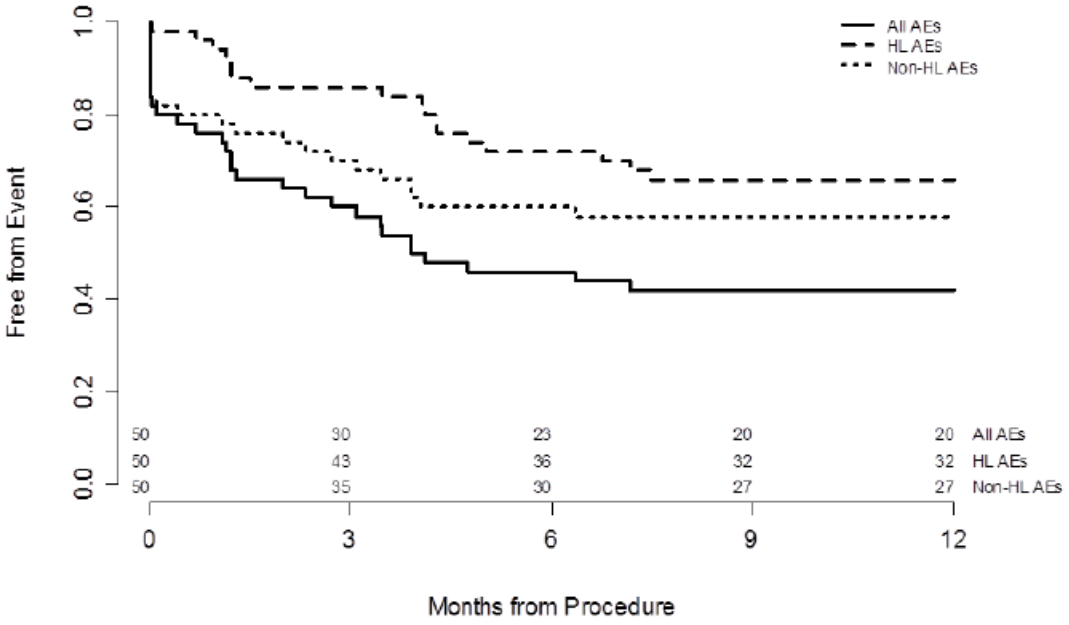
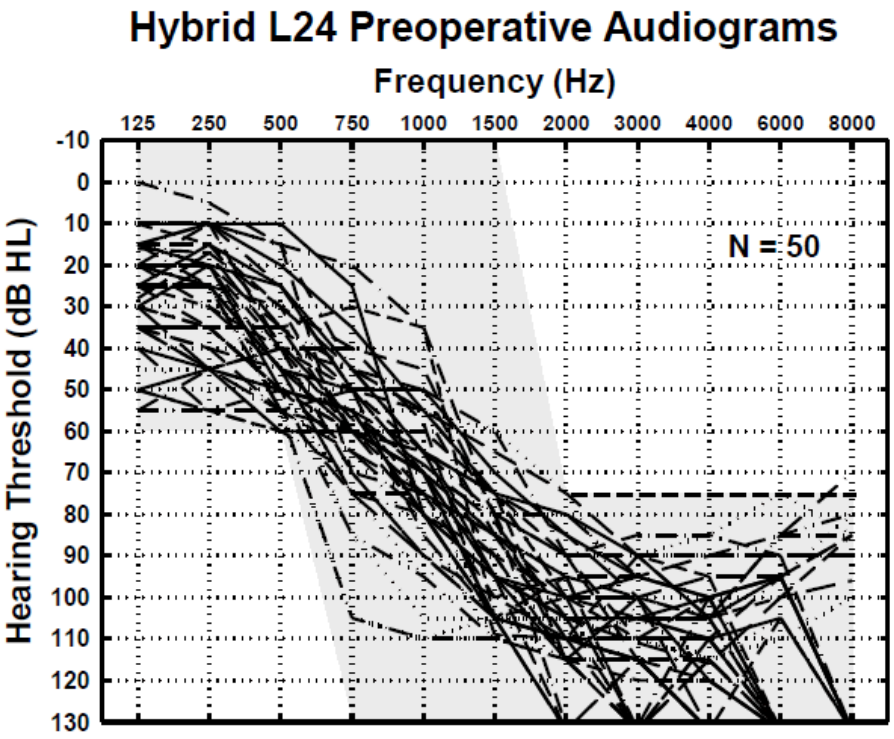


Figure 8: Kaplan-Meier curves for all adverse events reported, including those related to profound/total loss of hearing, and non-hearing related events



(Figure included from submission: Figure 13 of Volume 22)

Figure 9: Individual subjects' pre-operative audiometric thresholds



(Figure included from the submission, page 144 of 260, Volume 22)

Figure 10: CNC improvement versus amount of residual low-frequency hearing loss at 6 months

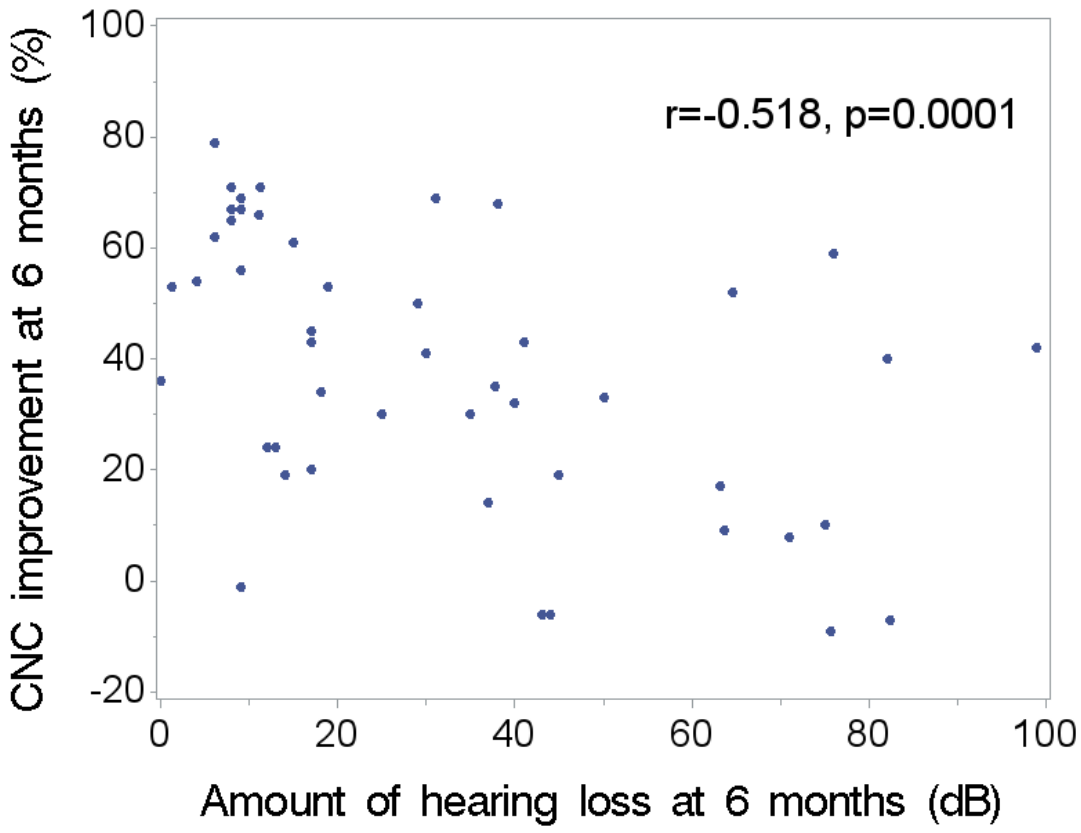


Figure 11: AzBio improvement versus amount of residual low-frequency hearing loss at 6 months

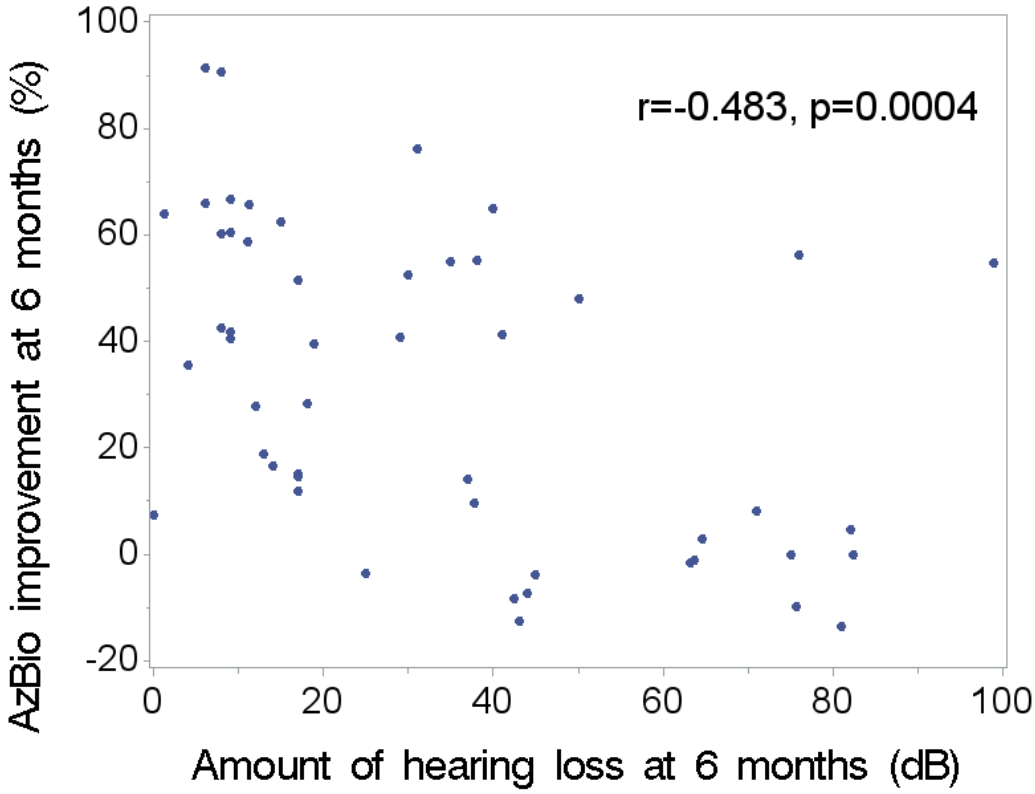


Figure 12: CNC improvement versus low-frequency hearing threshold at 6 months

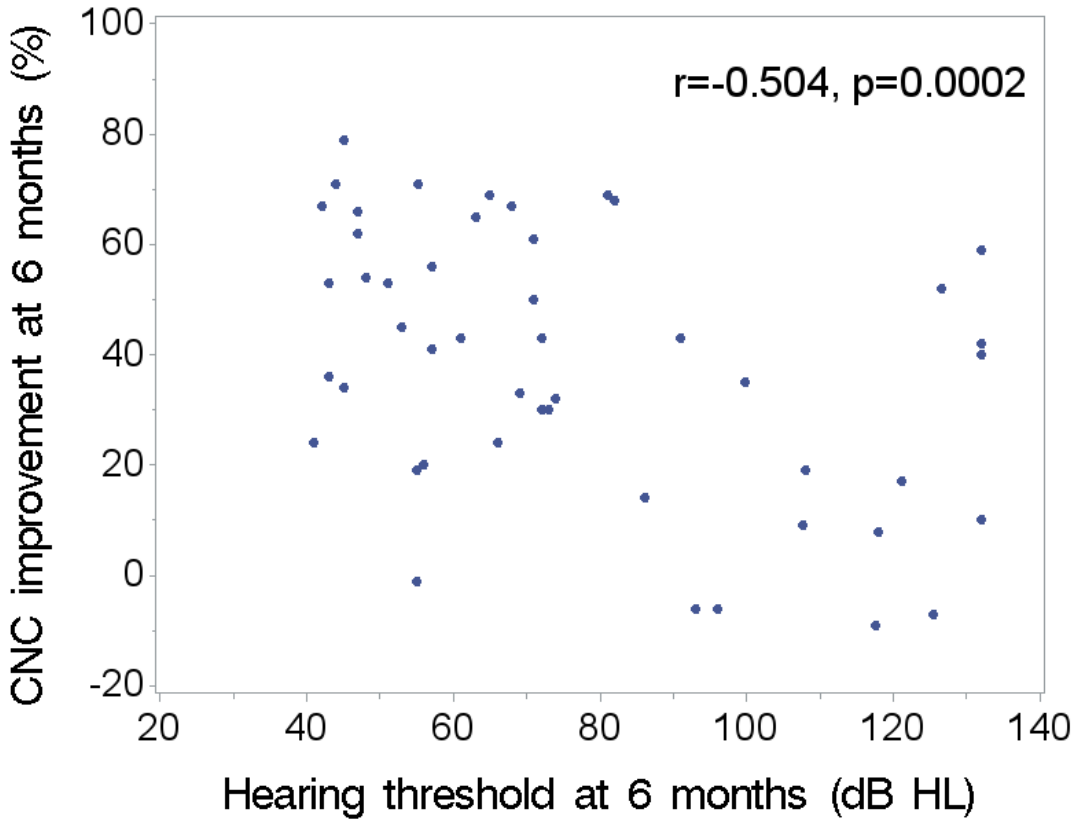


Figure 13: AzBio improvement versus low-frequency hearing threshold at 6 months