SPONSOR EXECUTIVE SUMMARY

NUCLEUS® HYBRID™ L24 IMPLANT SYSTEM

P130016

SEPTEMBER 27, 2013

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Terms, Acronyms, and Definitions

Acoustic Alone	Preoperative condition referring to the use of acoustic hearing, with or without amplification, ***ipsilateral*** to the implanted ear (i.e., in the same ear as the implant).
Acoustic Component (AC)	An optional component for the sound processor used with the Hybrid L24 implant, which provides amplification in the low frequencies for those patients who have residual hearing sensitivity postoperatively.
AzBio Test[1]	A sentence-level speech recognition test delivered in background noise, also utilized for this study.
Bilateral Acoustic	Preoperative condition referring to the use of ***bilateral*** acoustic hearing (i.e., acoustic hearing in both ears), with or without amplification.
BTE	Behind-The-Ear
CI	Cochlear Implant
CNC Word Recognition Test[2]	Consonant-Nucleus-Consonant Test; A monosyllabic word-level test given in quiet, which is calculated both as a word correct score and a phonemes correct score.
Device Use Questionnaire (DUQ)	"In-house" device usability metric, administered to determine subjective preferences and satisfaction with regards to device use in various listening environments.
E + A	Electric-acoustic stimulation
HL	Hearing Loss/Hearing Level
ITE	In-The-Ear

[1] Spahr, A.J., Dorman, M.F., Litvak, L.M., Van Wie, S., Gifford, R.,H, Loizou, P.C., Loiselle, L.M., Oakes, T., & Cook, S. (2011). Development and validation of the AzBio Sentence Lists, *Ear Hear*, 33(1): 112-117.
[2] Peterson, F.E. & Lehiste, I. (1962). Revised CNC lists for auditory tests. *J Sp Hear Dis*, 27(1): 62-70.

Terms, Acronyms, and Definitions

MAP	A program that defines the individualized fitting parameters of recipients for a specific speech coding strategy.
Musical Background Questionnaire (MBQ)	A self-assessment questionnaire that examined musical aspects of hearing.
National Acoustic Laboratories (NAL)	Refers to a procedure for appropriately fitting hearing aids.
Nucleus® Custom Sound™	Clinical programming software for Nucleus cochlear implant systems.
Nucleus® Freedom™ for Hybrid™ sound processor	BTE sound processor used in the Nucleus Hybrid L24 IDE clinical study; often abbreviated as "Freedom Hybrid sound processor" or "Hybrid sound processor."
RITE	Receiver-In-The-Ear.
Signal-to-Noise Ratio (SNR)	The level relationship (ratio) of the target (signal) to the noise (e.g., if the target speech is 60 dBA and the noise is 55 dBA then the SNR = +5 dB).
Speech, Spatial and Qualities of Hearing Scale (SSQ)	A validated metric used as a subject self-assessment of hearing in everyday life across three hearing domains: speech hearing, spatial hearing, and qualities of sound.
University of Washington Clinical Assessment of Music Perception[3] (UW-CAMP)	A test battery designed to provide an assessment of fundamental auditory skills important for music perception, consisting of three subtests: pitch perception, melody recognition and perception of timbre.

[3] Kang, S.Y., Nimmons, G.L., Drennan, W., Longnion, J., Ruffin, C., Nie, K., Won, J.H., Worman, T., Yueh, B., Rubinstein, J. (2009). Development and validation of the University of Washington clinical assessment of music perception test. *Ear Hear*, 30(4), 411-418.

Device-Use Configurations

- **Acoustic Stimulation**

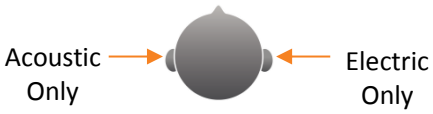
  Sound delivered acoustically alone on one or both sides, with or without amplification.

- **Electric Stimulation**

  Sound delivered via a cochlear implant alone.

- **Bimodal Mode**

  Use of acoustic hearing, with or without amplification, with electric hearing via electrical hearing via a cochlear implant on the *opposite* ear.

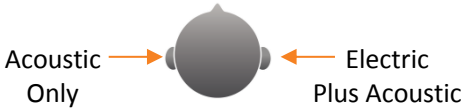


- **Hybrid Mode (Study Endpoint)**

  Use of acoustic hearing and electric hearing in the *same* ear.

- **Combined Mode (Everyday Use)**

  Use of acoustic hearing bilaterally, with or without amplification, in addition to electric hearing via a cochlear implant.



1. SUMMARY

1.1. Introduction

Over 36 million Americans are reported to have hearing loss. However, only 8.4 million actually have hearing aids, the treatment considered to be the standard of care. For the over 75% who do not seek treatment, the reasons vary from awareness of need to cost of ownership. Of those who have purchased a hearing aid, over 1 million report never using the hearing aids due to dissatisfaction with overall benefit, comfort, and performance in noise. More severe levels of hearing loss are treated with cochlear implants, the standard of care for bilateral severe to profound sensorineural hearing loss. Neither hearing aids nor cochlear implants are ideal for individuals who demonstrate normal to moderate low frequency hearing loss with a severe to profound sensorineural hearing loss in the high frequencies, more commonly known as a "ski-slope" hearing loss. Amplification does not adequately address the extensive high frequency loss that comes with ski-slope hearing loss. In addition, under current FDA-approved criteria, cochlear implantation is not an option.

The Nucleus Hybrid L24 Implant represents a new treatment option, the first truly integrated electric-acoustic solution, for individuals with ski-slope hearing loss. The device offers improvements in speech understanding that outweigh the risks associated with surgery and the potential degradation of acoustic hearing in the implanted ear. The clinical investigation of the Hybrid L24 is described in this document.

1.2. Indications for Use

The Nucleus® Hybrid L24 Implant System is intended for patients aged 18 years and 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 of candidates ranges from normal to moderate hearing loss in the low frequencies (thresholds no poorer than 60 dB HL up to and including 500 Hz), with severe to profound hearing loss at frequencies above 1500 Hz (threshold average of 2000, 3000, and 4000 Hz $\geq$ 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.

A typical Hybrid L24 patient profile is illustrated below in Figure 1.

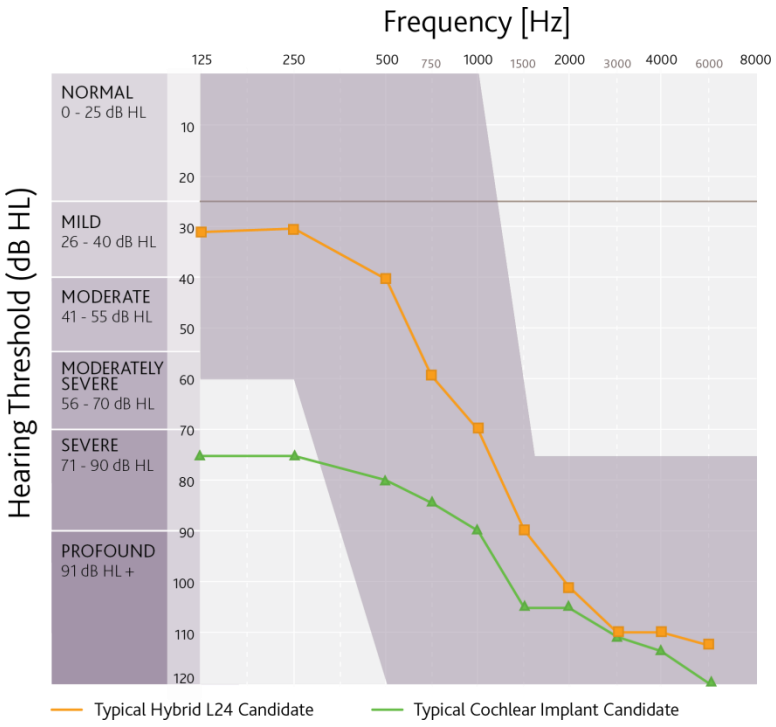


Figure 1: The typical patient profile of a Hybrid L24 candidate, indicated in the shaded region, and by the orange line. The green line indicates thresholds of a typical cochlear implant candidate.

A cochlear implant is not indicated for individuals who have the following conditions:

1. Deafness due to lesions of the acoustic nerve or central auditory pathway
2. Active middle ear infections
3. Absence of cochlear development
4. Tympanic membrane perforation in the presence of active middle ear disease.

1.3. Device Overview

The Nucleus Hybrid L24 Implant System is an electric-acoustic (E+A) stimulation system intended to address the needs of individuals who demonstrate normal to moderate low frequency hearing loss and severe to profound mid- and high frequency sensorineural hearing loss. The goal of the system is to provide electric stimulation to the mid- to high frequency region of the cochlea and acoustic amplification in to the low frequency regions, for patients with residual low frequency hearing sensitivity.

The Hybrid L24 system includes both implanted and external components (Figure 2). The implanted components of the system are:

- The Hybrid L24 Implant consisting of the Nucleus CI24RE receiver/stimulator assembly with the Hybrid L24 electrode array

The external components include:

- The Nucleus 6 (N6) sound processor with coil/cable, battery module, acoustic component and accessories
- Two user options for Remote Assistants

Figure 2: Hybrid L24 system components.

The internal components are identical to the Nucleus CI24RE cochlear implant available since 2005 (P970051/S028) with the exception of the intracochlear electrode array which is unique to this implant system.

The external components (with the exception of the acoustic component of the N6 sound processor) for the Hybrid L24 system are identical to those indicated for use with cochlear implants and approved in 2013 under P970051/S096.

The Hybrid L24 electrode array design and specifically its length and thin diameter, provides the best opportunity for potential preservation of low frequency hearing. Coupled with the N6 sound processor, which provides the unique combination of electric (for high frequencies) and acoustic stimulation (for low frequencies), the outcomes of this clinical study demonstrated:

1. that preservation of low frequency hearing sensitivity is possible,
2. that restoration of high frequency hearing via electric stimulation can significantly improve speech perception, and
3. that A+E hearing is superior to acoustic only or electric only hearing for those who maintain functional low frequency acoustic hearing.

1.4. Brief Description of Clinical Trial

1.4.1. Study Objective and Design

The objective of this multicenter pivotal study was to evaluate the safety and effectiveness of the Nucleus Hybrid L24 Implant System for the treatment of sensorineural hearing loss, characterized by a normal to moderate range in the low frequencies and a severe to profound loss in the high frequencies. The study employed a prospective, non-randomized, repeated-measures design, where each subject served as his/her own control. This allowed for comparison of preoperative performance with appropriately fit hearing aids and postoperative performance with the Nucleus Hybrid L24 Implant System.

Preoperatively, subjects were assessed in unaided and aided (in Acoustic Alone and Bilateral Acoustic) conditions. For candidacy assessment, subjects were tested with appropriately fit hearing aids (per the NAL prescription method) for aided testing. Aided speech perception scores also served as baseline measures for primary and secondary endpoint analyses. Pre- and postoperatively, subjects were assessed on measures of:

- hearing sensitivity,
- speech perception in quiet and in noise,
- music perception, and
- self-assessment questionnaires.

Upon implantation subjects were evaluated at 3, 6, and 12 months following activation of the implant. Unaided hearing thresholds for both ears were assessed at each test interval to monitor the impact of the implant surgery on residual hearing. Subjects continued to be seen semi-annually for monitoring of hearing sensitivity. All surgical or device-related adverse events were recorded throughout the study.

Various tests and listening conditions were used in this study to define overall outcomes for use of the device in various configurations. The two primary listening conditions discussed in this section can be found in Figure 3. For additional details regarding test procedures and materials please see Section 5 of this document.

- **Hybrid Mode (Study Endpoint)**

  Use of acoustic hearing and electric hearing in the *same* ear.

- **Combined Mode (Everyday Use)**
  Use of acoustic hearing bilaterally, with or without amplification, in addition to electric hearing via a cochlear implant.

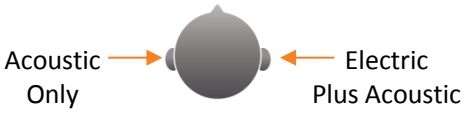


Figure 3: Primary device configurations used by the subjects.

1.4.2. Clinical Endpoints and Success/Failure Criteria

The interval for the primary clinical endpoint for efficacy analyses was at 6 months postactivation. Secondary endpoint measures were defined to reflect individual subject improvements and to lend consistency to the trial results. Safety data were collected for the duration of the study and reflected type and duration of adverse events.

Specifically, the two primary efficacy endpoints for this study were the assessment of statistical significance of the within-subject differences for two speech perception tests:

- Word recognition in quiet as evaluated with the Consonant-Nucleus-Consonant (CNC) Monosyllabic Word test,
- Sentence recognition in noise as evaluated with the AzBio test.

Scores on both speech tests were obtained at the 6 month postactivation interval for the implanted ear with the device in the Hybrid Mode, and compared to a preoperative Acoustic Alone Mode. The primary endpoints were that mean performance with each of these measures would show significant benefit with use of the Hybrid device compared with the preoperative Acoustic Alone condition in the implanted ear.

The co-secondary efficacy endpoints were also measured at the 6-month postactivation interval. Specifically, the secondary endpoint would be met if more than 75% of subjects scored equal to or better than the preoperative Acoustic Alone condition in the Hybrid Mode condition on the CNC word and phoneme measures, and if more than 75% scored equal to or better than the preoperative Acoustic Alone condition in the Hybrid Mode on the AzBio test.

1.4.3. Primary Efficacy Endpoint Analyses

The significance of the mean differences in speech perception scores between the preoperative and 6-month postoperative interval were analyzed using paired t-tests. The level of significance for these one-sided tests was 0.025. 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 were used.

1.4.4. Safety Data Analyses

All adverse events were tabulated for 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). This was compared qualitatively to previous cochlear implant studies. Time to first adverse event was summarized using Kaplan-Meier plots. Exploratory proportional hazards regression models were used to determine whether baseline factors were associated with risk for adverse events over the course of the study. Hazard ratios and 95% confidence intervals for these analyses were cited.

Individual hearing sensitivity levels were examined across test intervals to assess any changes and to characterize the impact of the procedure on low frequency hearing sensitivity.

1.4.5. Summary of Pivotal Study Results

1.4.5.1. Effectiveness

This clinical study demonstrated several benefits of the Hybrid L24 Implant System as compared to hearing aids for this type and degree of hearing loss, including improvements in word and phoneme understanding in quiet and sentence understanding in noise. Positive self-reported outcomes and increased satisfaction were observed in the majority of cases based on questionnaire data. These improvements are likely to be experienced by most individuals who meet the device's indications for use.

The study met its two primary and secondary efficacy endpoints. That is, the mean improvements observed pre- to postoperatively, were significant for both primary endpoint measures (CNC monosyllabic word recognition and AzBio sentence recognition in noise) for the implanted ear.

At 6 months postactivation:

- In the Hybrid Mode:
  - A statistically significant improvement ($p < 0.0001$) in word recognition in quiet at the 6-month endpoint was observed, with mean CNC monosyllabic word scores improving from 28.4% in the preoperative Acoustic Alone condition to 65.4% in Hybrid Mode.
  - A statistically significant improvement ($p < 0.0001$) in sentence recognition in a difficult noise environment (+5 dB SNR) at the 6-month endpoint was observed, with mean AzBio Sentence scores improving from 16.3% in the preoperative Acoustic Alone condition to 49.2% in Hybrid Mode.

Table 1: Primary efficacy endpoints met; statistical summary.

(N=49)#	Acoustic Alone Preoperative	Hybrid Mode 6 Months Postactivation	Percentage Point Change	P-Value*
	Mean ± S.D.	Mean ± S.D.	Mean ± S.D. (95% C.I)	
Word Scores	28.4% ± 14.7%	65.4% ± 25.4%	37.0 ± 26.6 (29.4, 44.6)	$p < 0.0001$
AzBio Scores	16.3% ± 14.4%	49.2% ± 30.8%	32.8 ± 29.1 (24.5, 41.2)	$p < 0.0001$

* Student's t-test p-value; signed-rank p-value if normality assumption failed.
# Subject [redacted] was reimplanted prior to the 6 month interval and was not included in the analyses, but is included in the mean scores preoperatively (N=50).

In addition, secondary endpoints were met in that more than 75% of the subjects implanted with the Hybrid L24 Implant System performed equal to or better than they did with an appropriately fit hearing aid preoperatively in the implanted ear (Acoustic Alone Mode).

Specifically:

- 98% (48/49) of subjects performed equal to or better postoperatively for CNC word recognition.
- 91.8% (45/49) of subjects performed equal to or better postoperatively for CNC phoneme recognition.
- 89.8% (44/49) of subjects performed equal to or better postoperatively for sentence recognition in noise at a +5 dB SNR as measured with AzBio sentences.

The primary endpoints of the study were specific to the Hybrid Mode (i.e., the implanted ear). However, this mode did not necessarily reflect an individual's true listening condition in everyday life. The study addressed this by testing subjects in the Combined Mode, which in all cases corresponded to the use of electric stimulation with all available acoustic hearing.

As shown in Figure 4, at 6 months postactivation, the subjects experienced:

- In the Combined Mode:
  - A statistically significant improvement ($p < 0.0001$) in word recognition in quiet at the 6-month endpoint, with mean CNC Word scores improving from 44.9% with the preoperative Bilateral Acoustic Mode, preoperatively to 79.4% in the Combined Mode.
  - A statistically significant improvement ($p < 0.0001$) in sentence recognition in a difficult noise environment (+5dB SNR) at the 6-month endpoint, with mean AzBio Sentence scores improving from 29.6% with the preoperative Bilateral Acoustic Mode to 62.6% in the Combined Mode.

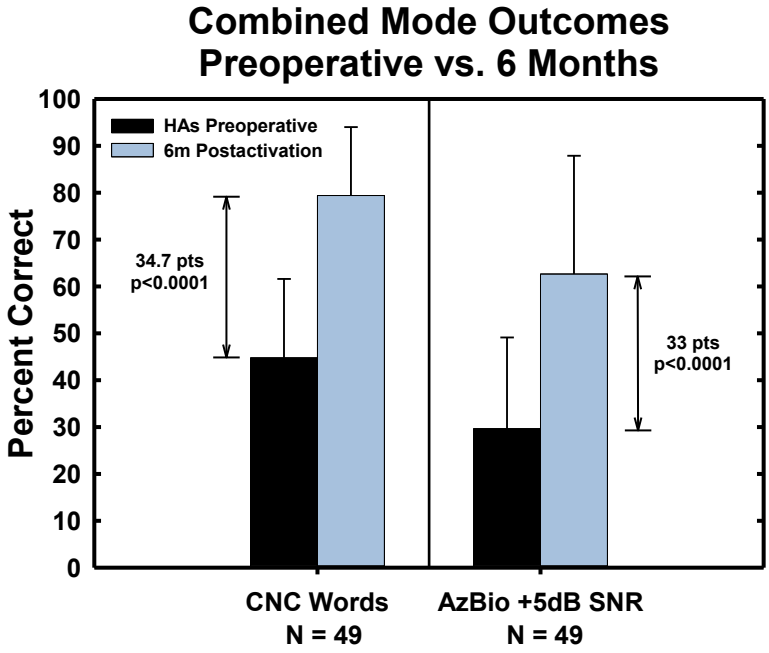


Figure 4: Mean pre- and postoperative outcomes for the CNC word recognition and AzBio in noise (+5 dB SNR) tests for the Combined Mode.

Self-Assessment Outcomes

Using the Hybrid L24 implant in their everyday listening mode, the subjects reported positive outcomes and increased satisfaction, in the majority of cases, based on

questionnaire data. On a validated self-assessment metric, the Speech, Spatial and Qualities of Hearing Scale (SSQ) most subjects reported subjective benefits and satisfaction across a range of conditions involving speech in quiet, noise and group settings, sound location and sound quality. There was a significant improvement in mean ratings for the three subscales of the SSQ, namely, Hearing for Speech, Spatial Hearing, and Qualities of Sound.

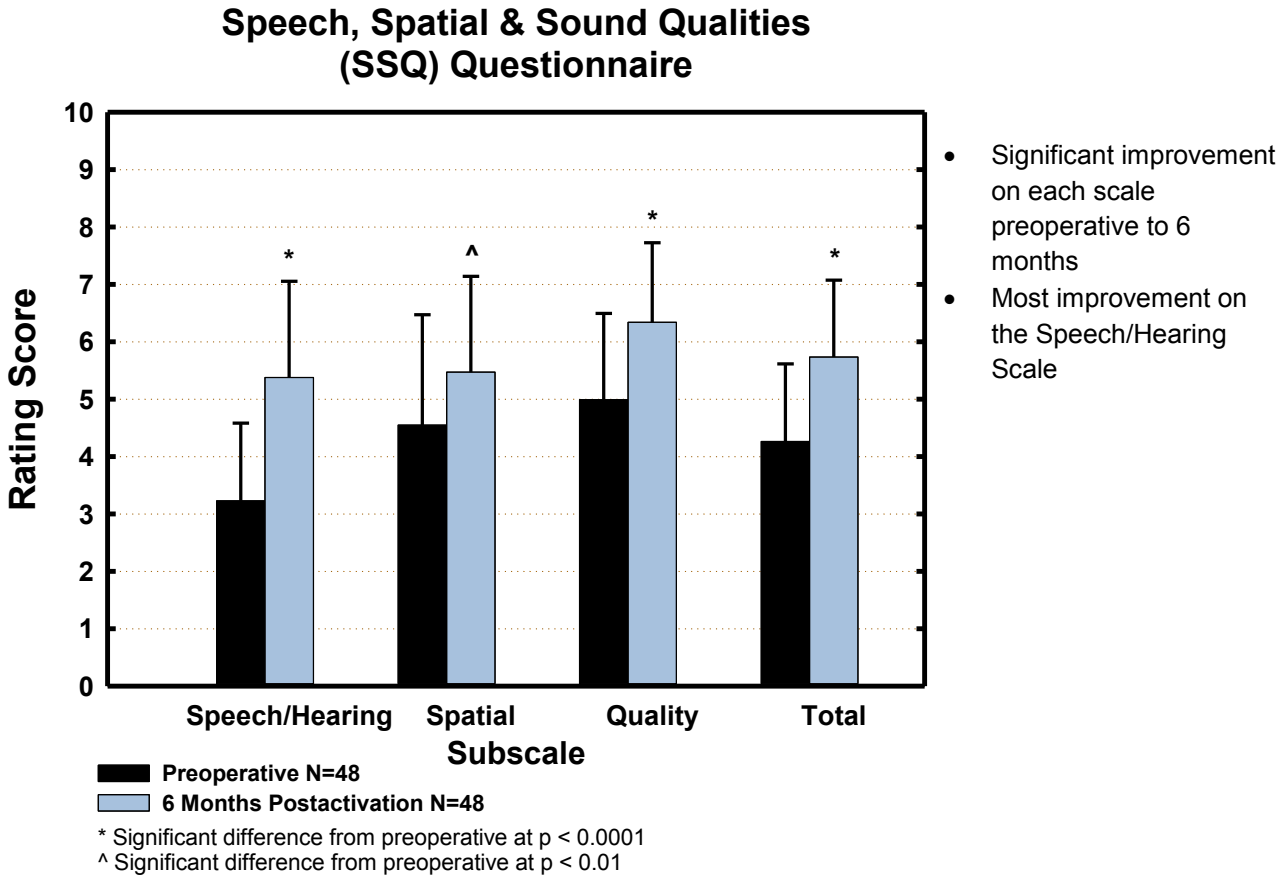


Figure 5: Mean SSQ Outcomes for Three Hearing Domains and Total Ratings.

Another important self-assessment outcome related to the subjects' satisfaction with both hearing aids and Hybrid L24 technologies. This was captured using the Device Usability Questionnaire (DUQ), copies of which can be found in the Appendices. Preoperatively, with hearing aids, 76% (38/50) reported being very dissatisfied/dissatisfied and only 8% (4/50) reported being very satisfied/satisfied with hearing aids. When asked the same question about the Hybrid L24, 79% (38/48) reported being very satisfied/satisfied and only 15% (7/48) reported being dissatisfied.

1.4.5.2. Safety

Sixty-five adverse events were reported during the course of the study. The type and frequency of the events were consistent with those reported in cochlear implantation or other mastoid operative procedures. None of the adverse events were determined to be serious in nature, and there were no unanticipated adverse device effects reported.

This study involved implanting subjects with functional low frequency hearing. Therefore unlike prior cochlear implant clinical trials, changes in hearing sensitivity were assessed and those that resulted in profound (> 90 dB HL) loss of low frequency hearing were also reported as anticipated adverse events.

Changes in low frequency hearing sensitivity at the 6-month study endpoint are summarized below:

- 33 subjects maintained hearing of a severe degree or better
- 17 experienced a decrease in low frequency hearing resulting in profound or total loss of hearing

As stated above, no subject, regardless of changes in low frequency hearing, showed a significant decrement in speech perception pre- to postoperatively in the Combined Mode (everyday condition), regardless of the level of postoperative hearing. Across frequencies, the largest drop in thresholds was seen at Initial Activation (4 weeks after surgery). Average thresholds at the 3, 6, and 12 month intervals are consistent across time intervals.

When evaluating preservation of hearing there are two definitions of significance.

1. Measurable – any measurable threshold(s) obtained
2. Functional – threshold(s) within a range that allows benefit from amplification (severe or better)

When applying these definitions to the 6 month outcomes of the Hybrid L24 dataset, 66% of the 50 subjects maintained functional hearing in the implanted ear; 90% maintained measurable hearing in the implanted ear and 100% had functional acoustic hearing when using both ears.

As documented in the clinical study results, a percentage of individuals will lose their preoperative low frequency acoustic hearing as a result of Hybrid L24 implant surgery. This known risk is disclosed in the Hybrid L24 implant system labeling and is strongly recommended as an integral component of preoperative surgical and device counseling. Irrespective of the postoperative hearing status, most individuals can still be expected to

receive substantial functional and speech recognition benefit on a daily basis when compared to preoperative Bilateral Acoustic Mode.

1.4.5.3. Summary and Conclusions

The Hybrid L24 Implant System represents a new treatment option, the first truly integrated electric-acoustic (E+A) solution, for a patient population that has few current therapeutic alternatives for ski-slope hearing loss. High frequency sound, crucial for speech discrimination, is provided electrically by the Hybrid L24 implant while low frequency hearing is amplified via the acoustic component. The two modes of stimulation are processed and provided simultaneously by the externally worn Nucleus 6 Sound Processor.

Subjects with ski-slope hearing loss who participated in the Hybrid L24 clinical study were able to combine both acoustic low and electric high frequency information, from one or both ears, provided by the Hybrid L24 Implant System. Results indicated significant speech perception improvements in quiet and in noise when compared to preoperative performance. In fact, the study met all efficacy endpoints, with adverse events occurring at a comparable rate to that of a typical cochlear implant population. At study endpoint (6 months postactivation):

- The mean score obtained by the subjects using the Hybrid L24 Implant System in the Hybrid Mode was significantly improved over the preoperative Acoustic Alone condition for CNC word recognition and AzBio sentence recognition in noise.
- 100% of subjects showed equal or greater speech perception performance when listening with both ears (Combined Mode).
- SSQ results across a large number of listening situations indicated a significant improvement on a group and individual subject basis with the Hybrid L24 Implant System compared to preoperative Bilateral Acoustic Mode.
- Finally, Hybrid implantation also provided an opportunity to maintain music perception abilities. On an assessment of music perception, Hybrid subjects maintained their music perception abilities on measures of pitch discrimination, familiar melody recognition, and timbre recognition.

2. BACKGROUND AND CURRENT THERAPIES

2.1. Background of a Cochlear Implant

Cochlear implants were initially approved in 1985 as a post-linguistic treatment option for adults with bilateral profound sensorineural hearing loss who received little or no benefit from amplification. With time cochlear implant criteria have broadened to include individuals with greater degrees of functional hearing, now including indications for both adults and children over 12 months of age with pre-, peri-, or post-linguistic bilateral moderate to profound sensorineural hearing loss who demonstrate limited functional benefit from amplification. The current indications were approved in 2005 (PMA # P970051/S028). Today, approximately 190,000 individuals benefit from Cochlear Nucleus technology.

A cochlear implant system has two primary components: an implant and an external sound processor with accessories (Figure 6). The sound processor captures sound, filtering, processing, and translating it into digital information which is transmitted to the implant. The implant contains a receiver/stimulator with an intracochlear electrode array. It is surgically placed in the mastoid space behind the ear with the electrode array inserted into the cochlea. The electrode array bypasses damaged hearing sensory cells, electrically stimulating the cochlea's spiral ganglion cells that innervate the auditory nerve.

1. The sound processor captures filters and processes sounds, translating them into digital information.
2. This digital information is transmitted from the sound processor to the internal receiver/stimulator.
3. The internal implant converts the information into electrical signals, sending them to a small electrode array positioned gently inside the cochlea.
4. The electrode bypasses the damaged hearing sensory cells, electrically stimulating the spiral ganglion cells in the cochlea that innervate the hearing nerve, thus allowing the brain to perceive sound.

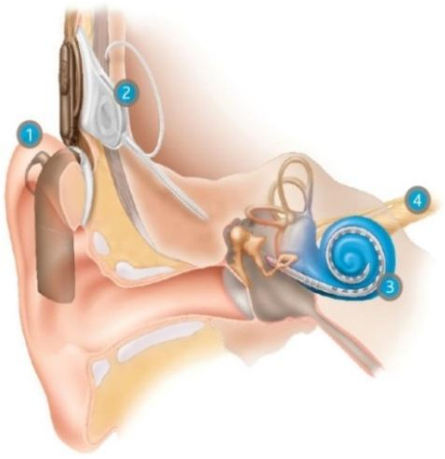
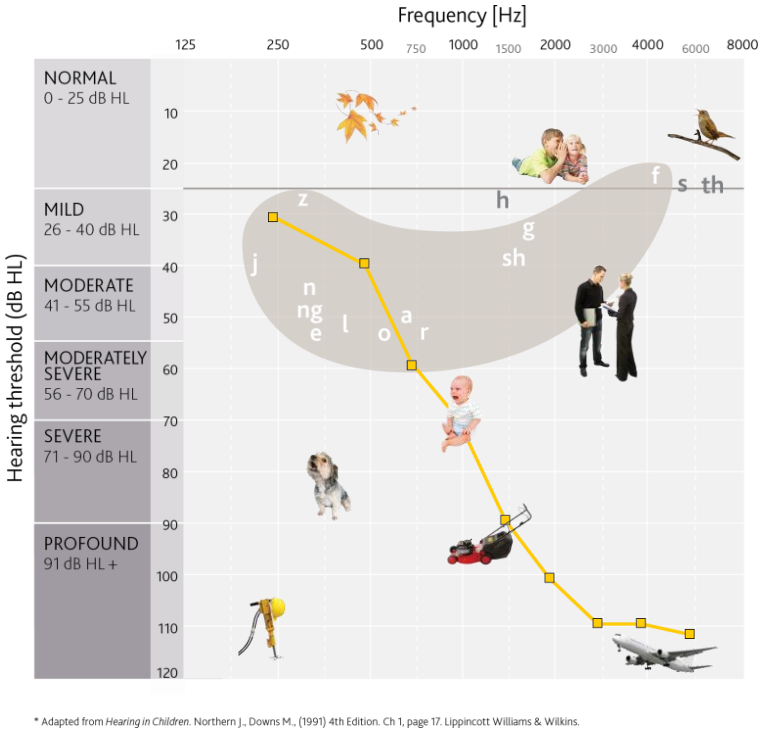


Figure 6: How a cochlear implant works.

2.2. Current Therapies for Sensorineural Hearing Loss

Sensorineural hearing loss is typically treated with conventional amplification, and with cochlear implants for more severe levels of hearing loss. Neither of these options is ideal for individuals with ski-slope loss.

Patients with ski slope loss currently have few effective therapeutic options; neither hearing aids nor cochlear implants alone are ideal. Amplification does not adequately address the extensive mid and high frequency loss; these individuals may not have functioning hair cells to make high frequency sounds meaningful, even if they could be made louder. Still, high frequency hearing is critical for speech intelligibility. Moreover, specialized amplification requires more advanced fitting approaches, and may be pushed to its technological limits, introducing other problems such as acoustic feedback and signal distortion. These problems underlie the typical reasons that amplification is abandoned. On the other hand, cochlear implantation does not take advantage of the substantial acoustic capacity these individuals may still have in the low frequencies, and, cochlear implants are not an option under current FDA-approved criteria.



* Adapted from *Hearing in Children*. Northern J., Downs M., (1991) 4th Edition. Ch 1, page 17. Lippincott Williams & Wilkins.

Figure 7: Audiogram depicting a ski slope audiogram with common sounds.

The audiogram shown in Figure 7 illustrates the types of common sounds that would be inaudible for candidates of a Hybrid L24 Implant. Figure 7 is representative of the typical audiometric profile of subjects in the pivotal study. Generally, in unaided

conditions, these individuals can to hear sounds "below the line" for the profile of loss described by the audiogram shown.

2.2.1. Frequency Lowering Hearing Aids

The hearing aid industry has endeavored to address the limitations of broadband hearing aids with the introduction of frequency lowering technology. Here, the design intention is to improve the audibility of high frequency information by "shifting" it into the lower frequency range. This means that high frequency speech sounds can be heard at lower frequencies where hearing is typically better.

Frequency lowering options have been available from various hearing aid manufacturers for some time. However, published outcomes are mixed and do not consistently demonstrate positive results[4][5][6].

2.2.2. Cochlear Implants

Some clinics have offered the cochlear implant as a treatment option for an individual with ski-slope hearing loss and poor speech discrimination. However, current cochlear implant systems have not been specifically designed to preserve low frequency acoustic hearing.

2.2.3. The Hybrid L24 Implant System

As neither electric (cochlear implant) nor acoustic (hearing aid) treatment alone has adequately addressed the needs of this hearing impaired population, clinical research moved in the direction of a combined treatment. Research has confirmed that the potential to provide acoustically useful low frequency hearing can lead to benefits in music appreciation and in sound localization, where providing access to high frequency information improves speech perception (clarity), especially in difficult listening

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[4] Kang, S.Y., Nimmons, G.L., Drennan, W., Longnion, J., Ruffin, C., Nie, K., Won, J.H., Worman, T., Yueh, B., Rubinstein, J. (2009). Development and validation of the university of Washington clinical assessment of music perception test. *Ear Hear*, 30(4), 411-418.
[5] McDermott, H. The Benefits of Nonlinear Frequency Compression for a Wide Range of Hearing Losses. *Audiology Online*. 11 January 2010.
[6] Perreau, AE, Bentler, RA, Tyler RS (2013). The contribution of a frequency-compression hearing aid to contralateral cochlear implant performance. *J of Am Ac Audiol*. (2):105-20.

conditions[789]. Figure 8 explains the advantages of combining electric and acoustic information simultaneously in the same ear.

Acoustic: Maintain low-frequency acoustic hearing

- More natural sound quality
- Easier to understand speech in noise
- Better music appreciation

Electric: Restore high-frequency sensitivity

- Better speech perception; clarity
- Access to the full spectrum of sound

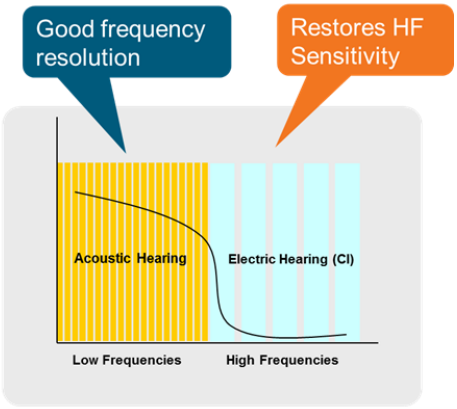

Figure 8: Benefits of electric-acoustic (E+A) hearing.

In 2003, Cochlear and leading researchers began working together with the product design goal of advancing E+A stimulation (e.g., Gantz & Turner, 2003; Gantz & Turner, 2004; Gantz et al., 2005, 2006; Gfeller et al., 2006; James et al., 2005, 2006; Luetje, et al., 2007; Turner et al., 2004). Over the next 10 years, Cochlear studied a variety of electrode array designs with the aim of developing a solution that optimized speech perception compared to cochlear implants, while preserving low frequency acoustic hearing. The Hybrid L24 implant is the result of that extensive research. The development of a sound processor that was capable of delivering both acoustic and electric stimulation was also key. The first generation sound processor that was used as part of this clinical study was introduced in 2007. A second generation sound processor (Nucleus 6) was developed in 2012.

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[7] Gantz, B. J., Turner, C., & Gfeller, K. E. (2006). Acoustic plus electric speech processing: preliminary results of a multicenter clinical trial of the Iowa/Nucleus Hybrid implant. *Audiol Neurootol*, 11 Suppl 1, 63-68.
[8] Gfeller, K. E., Olszewski, C., Turner, C., Gantz, B., & Oleson, J. (2006). Music perception with cochlear implants and residual hearing. *Audiol Neurootol*, 11 Suppl 1, 12-15.
[9] Dunn, C. C., Perreau, A., Gantz, B., & Tyler, R. S. (2010). Benefits of localization and speech perception with multiple noise sources in listeners with a short-electrode cochlear implant. *J Am Acad Audiol*, 21(1), 44-51.

In order to fully appreciate the difference between the population studied and a typical cochlear implant candidate, the audiometric and speech discrimination profiles for both a Hybrid L24 and a Nucleus cochlear implant are displayed in Figure 9. The populations' preoperative audiometric and speech perception capabilities (with hearing aids) differ significantly along with their performance expectations from an implantable hearing device.

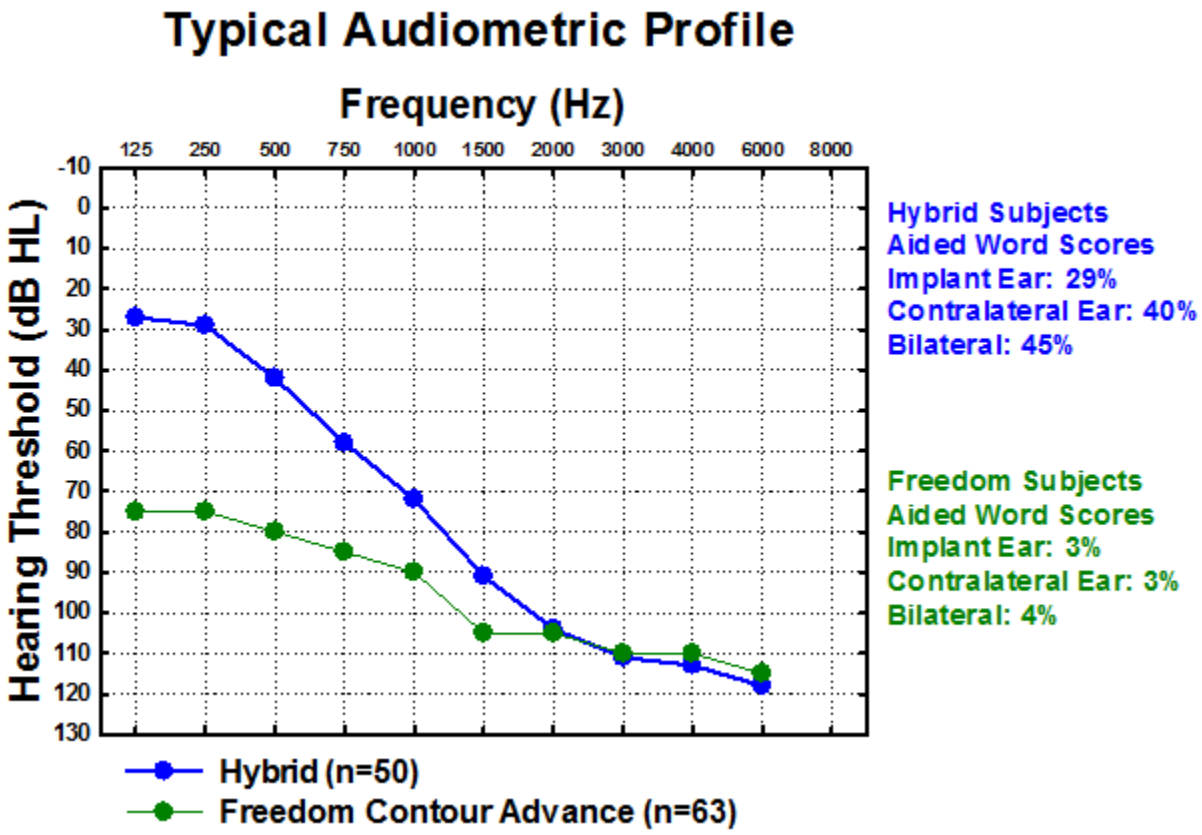


Figure 9: Average preoperative audiometric configuration and speech perception performance for subjects enrolled the Hybrid L24 and Cochlear Nucleus Freedom clinical trials.

Over of the last six years, the Hybrid L24 Implant System underwent extensive clinical validation at multiple international implanting centers. Outcomes from those trials are summarized in Section 8; these support the safety and effectiveness of the Hybrid L24 Implant System for its intended use.

In addition to the clinical study of the Hybrid L24 used to support this application, Cochlear has conducted studies pertaining to E+A stimulation with shorter electrode arrays. The implants in these studies used electrode arrays that have a shorter length and

fewer active intracochlear electrodes than does the Hybrid L24. The unpublished data from these other Hybrid cochlear implant clinical studies are summarized in Section 8.

3. DEVICE AND PROCEDURE DESCRIPTION

The Nucleus Hybrid L24 Implant System is an electric-acoustic (E+A) stimulation system intended to address the needs of ski-hearing loss individuals who demonstrate normal to moderate low frequency hearing sensitivity, but who have severe to profound mid- and high frequency sensorineural hearing loss.

3.1. Hybrid L24 System Components

The system includes both implanted and external components for patient use (Figure 10) and software and an intraoperative remote assistant for professional/clinician use. The distinctive Hybrid L24 electrode array design, and specifically its length and thin diameter, provides the opportunity for preservation of low frequency hearing. The N6 sound processor is capable of providing acoustic amplification for low frequencies, and electric stimulation for high frequencies. This unique combination enables the Hybrid System to provide the best option to balance hearing preservation in the low frequencies while maximizing performance with the combination of electric-acoustic stimulation.

Figure 10: Hybrid L24 System patient use components.

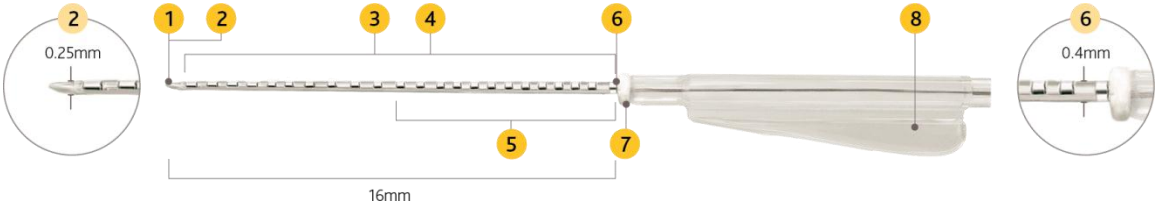
3.1.1. The Hybrid L24 Implant (Patient Use)

The implanted components of the system are the Hybrid L24 Implant that consists of the Nucleus CI24RE receiver/stimulator assembly with the Hybrid L24 electrode array. With the exception of the intracochlear electrode array which is unique to this implant system, the internal components are identical to the Nucleus CI24RE cochlear implant currently available since 2005.

The Hybrid L24 Implant (model CI24REH) consists of the Nucleus Freedom receiver/stimulator assembly with the unique Hybrid L24 electrode array. While the

Hybrid L24 electrode array has 22 active electrodes like Cochlear's conventional electrode arrays; it is shorter and thinner with the intention of preserving the integrity of the apical region of the cochlea.

The electrode array of the Hybrid L24 Implant has an approximate total length of 16 mm from the soft tip back to the 'stopper' that controls insertion depth and is designed for lateral wall placement. Figure 11 provides the specifications of the electrode array.



1. Soft-tip for minimal insertion trauma
2. Diameter at apical end: 0.25mm
3. 22 platinum electrode contacts spread across 14.5mm active length
4. Half-band intracochlear electrode array with small lateral surface
5. Basal stiffener prevents buckling
6. Diameter at basal end: 0.4mm
7. Stopper controls insertion depth
8. Handle provides reliable electrode orientation, fixation, and surgical handling

Figure 11: Features of the Hybrid L24 electrode array.

3.1.2. How the Hybrid L24 Electrode Works

Figure 12 illustrates how the Hybrid electrode functions within the cochlea. Color coding shows that low frequency sounds stimulate the apical region and high frequency sounds stimulate the basal region. The Hybrid L24 electrode array is designed to be inserted partially into the cochlea, treating high frequency hearing loss while preserving the structures responsible for low frequency hearing.

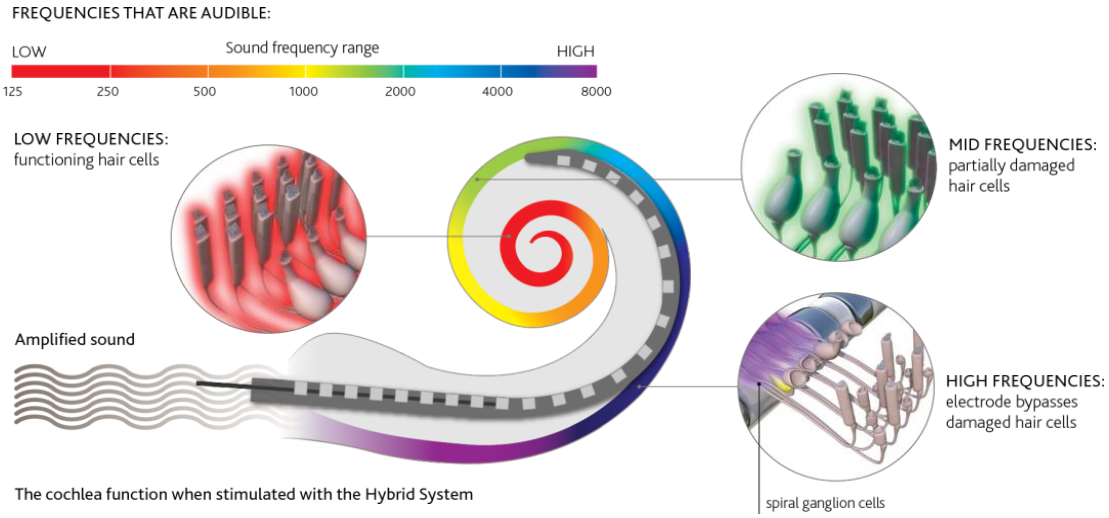


Figure 12: How the Hybrid L24 electrode array works.

3.1.3. Nucleus 6 Sound Processor and Remote Assistant (Patient Use)

The external components include:

- The Nucleus 6 (N6) sound processor with coil/cable, battery module, acoustic component and accessories
- Two user options for the Remote Assistant

There are two N6 sound processor models (CP910/920), which are identical except that the CP920 does not have a port to use with accessories. Of the two remote assistant models available for patient use; the CR210 has basic functionality and the CR230 has full functionality.

With the exception of the acoustic component of the N6 sound processor, the external components are identical to those indicated for use with cochlear implants and approved in 2013 in the United States.

NOTE: The clinical trial of the Hybrid L24 implant system used an early generation sound processor, the Freedom Hybrid Sound Processor, which was found to be equivalent to the Nucleus 6 Sound Processor.

3.1.4. Programming Components (Clinician Use)

A third remote, available only for use by clinicians in the operating room, is the model CR220 Intraoperative Remote Assistant.

Programming of the Hybrid L24 System is accomplished using specific Custom Sound Suite software. This software allows the clinician to easily integrated programming of both the electric and acoustic features of the N6 Sound Processor. This next generation software is based on cochlear programming software used during the last decade in Cochlear Nucleus products.

3.2. Hybrid Sound Processor Programming

As described earlier, the Hybrid sound processor permitted acoustic stimulation to be provided via an auxiliary acoustic module, called the Acoustic Component (AC), supplementary to electric stimulation. The Hybrid AC connected to the sound processor via a cable molded into the earhook of the processor, thereby delivering acoustic amplification in a similar way to a conventional hearing aid.

The goal of the programming approach, as implemented in the Custom Sound software, was to assign acoustic frequency channels to regions of functional acoustic hearing. For the purposes of programming, "functional" acoustic hearing was defined by audiometric thresholds better than 90 dB HL. Frequency assignment of the electric channels began at the frequency where acoustic hearing was deemed nonfunctional (i.e., 90 dB HL or poorer). For example, as illustrated in Figure 13, if the subject's hearing in the implanted ear was 90 dB HL or poorer for frequencies at and above 1000 Hz (i.e., functional acoustic hearing up to 750 Hz), the lower frequency boundary for electric stimulation was automatically set by the software to deliver electric stimulation just above 750 Hz through 7938 Hz. Frequency channels that included 750 Hz and below were reserved for acoustic amplification.

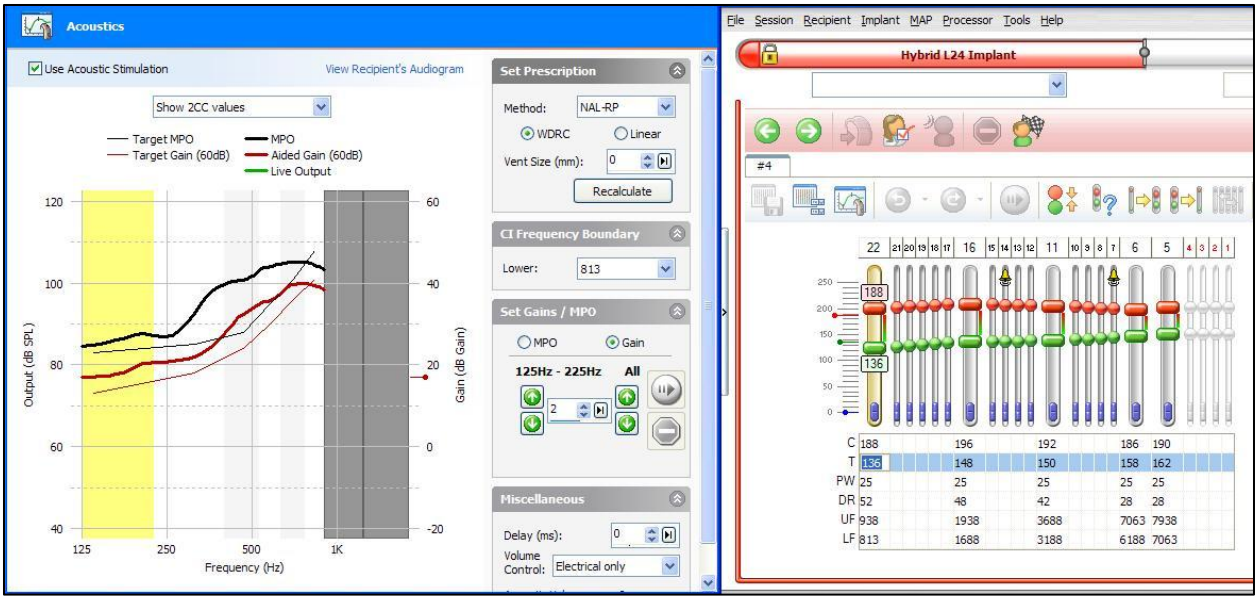


Figure 13: Sample screenshot of Custom Sound with parameters set for an individual with functional acoustic hearing through 750 Hz. Acoustic channels are enabled up to 813 Hz (i.e., up to and including 750 Hz) as shown on the left. Electric channels are assigned to frequency bands from 813 Hz through 7938 Hz.

3.3. Surgical Procedure Overview

The surgical procedure for the Nucleus Hybrid L24 cochlear implant is similar to that used for the Nucleus 24 cochlear implant. The incision, mastoidectomy and facial recess approach are identical. Additional care is taken to make a small 0.75 mm cochleostomy by first saucerizing down to the level of the endosteum and then opening the endosteum with a pick, inferiorly and slightly anteriorly to round window. Suctioning of any intracochlear fluid is avoided. The electrode array is then inserted 16 mm into the scala tympani instead of the more typical 19 to 24 mm (depending on specific design and surgical technique used) in more traditional electrode array insertions. Intraoperative impedance telemetry was performed to verify electrode array integrity. After placement and securing of the receiver/stimulatory, the incision is closed and the patient is activated approximately one month after surgery.

4. SUMMARY OF PRECLINICAL STUDIES

The Nucleus Hybrid L24 Implant System represents modifications to the currently marketed Nucleus 24 Cochlear Implant System. The required preclinical testing (biocompatibility, electrical, environmental, EMC, EMI, mechanical and sterilization) was conducted in compliance with applicable national and international regulations and was found to meet or exceed the required acceptance criteria.

Because the Nucleus Hybrid L24 Implant System represents modifications to the currently marketed Nucleus 24 Cochlear Implant System, the non-clinical studies that were undertaken to evaluate the safety and effectiveness of the Hybrid L24 relate to the following components:

- New Intracochlear electrode array.
- Nucleus 6 Sound Processor.
- New Remote Assistants.

The results of the non-clinical studies are summarized below and demonstrate, with a reasonable level of assurance, that the components meet or exceed the preclinical requirements for its intended use.

4.1. Intracochlear Electrode Array

4.1.1. Temporal Bone Insertion Studies

Hybrid L24 intracochlear electrode arrays were inserted into multiple temporal bones that were subsequently processed for histological assessment and showed no evidence of trauma. Results also showed minimal resistance upon electrode insertion, ease of full insertion and lack of proximal electrode "buckling." The electrode was found to meet all temporal bone performance requirements.

4.1.2. Mechanical Robustness and Environmental Testing

The Hybrid L24 intracochlear electrode array was subjected to the following mechanical robustness testing and passed or exceeded all acceptance criteria:

- Linear and Angular Fatigue Test of the Electrode Array.
- Severe Stress and Twist of the Electrode Lead.
- Severe Electrode Lead Shear Test.

As the Hybrid L24 implant uses the same stimulator and coil assembly as the CI24RE cochlear implant, environmental tests performed on the CI24RE were appropriately applied to the Hybrid L24 implant. The only difference between the two implants (the intracochlear electrode array) had no impact on the environmental test results.

4.1.3. Charge-Density Calculations

Taking into account the area and periphery of the smallest electrode surface, charge density calculations were completed to assure safe current stimulation by electrodes in the cochlea.

4.2. Nucleus 6 Sound Processor and Remote Assistants

External components and remote assistants were subject to the following testing and all pre-specified acceptance criteria were met:

4.2.1. Mechanical Robustness and Environmental Testing

- Cold Test
- Dry Heat
- Thermal Cycling
- Cyclic Damp
- Low Pressure
- Random Vibration
- Free Fall
- Ingress Protection Testing
- Clamp Force
- Overmold Strength Test
- Retention Tests
- LED Light Test

4.2.2. Electrical Testing – Nucleus 6 Sound Processor

External components underwent the following testing and all pre-specified acceptance criteria were met.

- Electrical Basic Functionality
- RF Link Electrical Verification
- Mobile Phone Compatibility and RF Immunity

- Radio Testing
- EMC
- Wireless Range

4.2.3. Electrical Testing – Remote Assistants

The Remote Assistants underwent the following testing and all pre-specified acceptance criteria were met.

- Basic Functionality
- EMC
- Wireless Link, Immunity to RF
- Wireless Range Verification
- Radio Compliance

4.2.4. Lithium Ion Battery Testing

The device's lithium ion battery underwent the following test and all acceptance criteria were met.

- UL 1642
- IEC 62133

4.3. Hybrid L24 End to End Acoustic Verification Testing

End-to-end testing including electrical and acoustical verification, acoustical system behavior, and listening tests were completed to verify that the Hybrid L24 system functions as intended. The acoustical testing characterization was done in accordance of ANSI S3.22: 2009. Results demonstrate that the System functions as intended and is acceptable for clinical use.

4.4. Hybrid L24 Freedom and N6 sound Processor Equivalency Testing

Comparison bench testing between the Freedom Hybrid processor (used in the clinical study) and the Nucleus 6 processor was conducted. Testing showed that the function and acoustic output of the two processors used in Hybrid mode were found to be equivalent or better in the case of the Nucleus 6.

4.4.1. Biocompatibility

4.4.1.1. Intracochlear Electrode Array

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

4.4.1.2. Nucleus 6 Sound Processor and Remote Assistants

Biocompatibility/biological tests were conducted on the new materials/processes of the Nucleus 6 and remote assistants in accordance with ISO 10993-5 and ISO 10993-10. No failures were observed therefore the materials contained within the components were considered safe for use.

4.4.2. Sterilization

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

5. PIVOTAL STUDY PROTOCOL SUMMARY

5.1. Study Objective and Design

The objective of this multicenter pivotal study was to evaluate the safety and effectiveness of the Nucleus Hybrid L24 Implant System for the treatment of sensorineural hearing loss, characterized by a normal to moderate range in the low frequencies and a severe to profound loss in the high frequencies. The study employed a prospective, non-randomized, repeated-measures design, where each subject served as his/her own control. This allowed for comparison of preoperative performance with amplification and postoperative performance with the Nucleus Hybrid L24 Implant System. Subjects were assessed with and without use of an additional hearing aid in the contralateral (unimplanted) ear.

The null hypothesis tested for the primary effectiveness endpoint was that there was no difference between pre- and postoperative speech performance, as measured by the CNC Monosyllabic Word Recognition Test and the AzBio Sentence Test in noise. 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.

Individual audiometric data were examined across test intervals to assess any changes in hearing sensitivity and to characterize the impact of the procedure on residual hearing sensitivity in the low frequencies.

5.1.1. Primary Objectives

Efficacy Objective 1 – CNC Word Recognition

Objective:

The objective was to demonstrate that mean word recognition as delivered by the Hybrid L24 implant system in the Hybrid Mode[10] (i.e., electric + acoustic) was significantly better

[10] So that outcomes for all subjects were accounted for in the event that a subject experienced a change in hearing resulting in nonuse of the Acoustic Component scores obtained with Electric Stimulation only were substituted.

than that observed preoperatively with the subjects using Acoustic Alone (i.e., hearing aid) in the implant ear.

Endpoint:

Comparisons were made between preoperative CNC word scores (Acoustic Alone) and 6-month postactivation scores (Hybrid Mode) for the treated ear.

Hypothesis:

The null hypothesis tested was that there was no difference for the subjects between pre- and postoperative speech performance, as measured by the CNC Word Recognition Test.

Efficacy Objective 2 – AzBio Sentence Recognition in Noise

Objective:

The objective was to demonstrate that mean sentence recognition in noise as delivered by the Hybrid L24 implant system in the Hybrid Mode (i.e., electric + acoustic stimulation) was significantly better than that observed preoperatively with the subjects using Acoustic Alone (i.e., hearing aid).

Endpoint:

Comparisons were made between preoperative AzBio sentence scores (Acoustic Alone) and 6-month postactivation scores (Hybrid Mode) for the treated ear.

Hypothesis:

The null hypothesis to be tested was that there was no difference for the subjects between their pre- and postoperative speech performance, as measured by AzBio sentences in noise.

5.1.2. Primary Safety Objective

Objective:

The objective was to describe the safety of implantation with the Nucleus Hybrid L24 Implant System.

Endpoint:

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 with corresponding 95% exact binomial confidence limits and the number of events per

patient-time (e.g., events per 10 patient years). Time to first adverse event was summarized using Kaplan-Meier estimated survival curves. Exploratory proportional hazards regression models were used to determine whether baseline factors were associated with risk for adverse events over the course of the study. Hazard ratios and 95% confidence intervals for these analyses were cited.

Hypotheses:

Since this objective was to characterize the adverse events observed, no formal hypotheses were made.

5.1.3. Secondary Objectives

Secondary efficacy endpoints (based on the performance in the Hybrid Mode, treated ear) were as follows:

- On the CNC word measure, most (> 75%) of the subjects scored equal to or better than they did in the preoperative Acoustic Alone condition;
- On the CNC phoneme measure, most (> 75%) of the subjects will scored equal to or better than they did in the preoperative Acoustic Alone condition; and
- On the AzBio sentences-in-noise measure, most (> 75%) of the subjects scored equal to or better than they did in the preoperative Acoustic Alone condition.
- Individual scores obtained at 6 months were compared with those obtained, on the same measures preoperatively, based on binomial comparisons[11].

5.1.4. Study Population

Individuals who presented with the above described hearing loss and met the specific inclusion/exclusion criteria were included in the study.

Criteria for Inclusion:

1. Eighteen years of age or older at the time of implantation.

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[11] Thornton, A.R. & Raffin, M.J.M. (1978). Speech discrimination scores modeled as a binomial variable. *J Sp Hear Res*, 21: 507 518.

2. Severe to profound (a threshold average of 2000, 3000, & 4000 Hz ≥ 75dB HL) sensorineural hearing loss for frequencies > 1500 Hz. 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% ≤ score ≤ 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.

Criteria for Exclusion:

1. Duration of severe to profound hearing loss > 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, in the range 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.
11. Additional handicaps that would prevent or restrict participation in the audiological evaluations.

5.1.5. Brief Summary of Treatment and Follow-up Protocols

Preoperatively, candidates were assessed in unaided and aided (Acoustic Alone and Bilateral Acoustic) conditions, to evaluate their appropriateness for entrance into the study and to establish baseline measures. In order to assure appropriateness of fit, all hearing aids fittings met NAL prescriptive targets.[12] Subjects underwent a 14-day hearing aid trial to allow acclimatization, in the event that a new hearing aid fitting or adjustment was required. Pre- and postoperatively, subjects were assessed on measures of speech perception in quiet and in noise, music perception and completed self-assessment questionnaires. Unaided hearing thresholds for both ears were assessed at each test interval to monitor the impact of the implant surgery on residual hearing.

Table 2 provides an overview of assessments conducted per interval over 12 months of the study. Subjects continued to be seen semi-annually for monitoring of audiometric thresholds.

Table 2: Study assessments as a function of study evaluation interval.

	Baseline Evaluation	Initial Device Activation	3 Months Post-activation	6 Months Post-activation	12 Months Post-activation	Bi-annual
Informed Consent	X					
Medical and Hearing History	X					
Verification of Hearing Aid Function	X		X¥	X¥	X¥	
Unaided Hearing Thresholds and Tympanometry	X	X	X	X	X	X
Aided Audiometric Thresholds	X	X	X¥	X¥	X¥	
Aided CNC test in quiet	X	X	X	X	X	
Aided AzBio sentences-in-noise test	X		X	X	X	

[12] Consistent with current hearing aid fitting procedures, deviation from NAL derived targets was permissible to address individual listening needs (e.g., to address occlusion or sound quality effects).

	Baseline Evaluation	Initial Device Activation	3 Months Post-activation	6 Months Post-activation	12 Months Post-activation	Bi-annual
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	

¥ In the event that a change in hearing > 10 dB at two or more frequencies occurred since previous visit.

5.1.6. Test Materials and Evaluation Intervals

A comprehensive set of test materials were used to assess hearing sensitivity, speech perception, self-assessment of hearing, and the fundamental auditory skills important for music perception. All of the auditory test battery materials are validated tests commonly used in cochlear implant and/or hearing aid research. The test materials were administered in multiple hearing modes that measured outcomes in Acoustic Alone, Bilateral Acoustic, Hybrid, and Combined Modes. Subjects were tested using a configuration where the loudspeaker delivering the target speech was at 0º azimuth.

CNC Monosyllabic Word Recognition Test (Primary endpoint)

The CNC Monosyllabic Word Recognition Test is a measure of open-set word recognition consisting of 10 recorded lists of 50 monosyllabic words (consonant-nucleus-consonant) such as ‘laud’ and ‘duck’. Two lists were administered in quiet at 60 dBA in the sound field and reported as percent correct for words and phonemes.

AzBio Sentence Test (Primary endpoint)

The AzBio Sentence Test is a measure that consists of 33 lists of 20 sentences (such as “He cried when the pet goat was sent to market.”) that contain low contextual information. Each list includes 5 sentences from each of 4 different speakers (2 male, 2 female). Two lists of the AzBio sentences were presented at 60 dBA with competing noise (babble) presented at a level to achieve a +5 dB signal-to-noise ratio from the same loudspeaker.

University of Washington Clinical Assessment of Music Perception (UW-CAMP)

The UW-CAMP test consists of 3 subtests each designed to provide an assessment of fundamental auditory skills important for music perception. The three subtests were presented at 65 dBA and provided an assessment of pitch perception, melody recognition and timbre.

The Speech, Spatial, and Qualities of Sound Questionnaire (SSQ)

The SSQ is a validated self-assessment metric commonly used in hearing aid and cochlear implant research. It is designed to measure self-reported auditory disability across a wide variety of domains, reflecting the reality of hearing in the everyday world. There are 49 questions scored by the subject using a scale of 0 through 10, where 0 corresponded to minimal ability and 10 corresponded to complete ability. There are three specific hearing domains assessed:

- Speech hearing scale – hearing speech in quiet and in noise, one-on-one conversation and in groups/meetings,
- Spatial hearing scale – hearing where sounds are coming from, distance, movement, and ability to segregate sounds,
- Qualities of sound scale – ease of listening, naturalness, clarity, identification of different speakers, musical pieces and instruments as well as everyday sounds.

Device Use Questionnaire (DUQ)

This questionnaire (~90 questions) was developed by Cochlear and is used to collect information regarding device usability, subjective preferences and satisfaction with regards to device use in various listening conditions.

Musical Background Questionnaire (MBQ)

A self-assessment questionnaire that examined musical training prior to hearing loss, listening habits, satisfaction with music listening, quality of music, enjoyment of musical styles, enjoyment of different instrumental timbres.

Audiometric Thresholds

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.

Unaided testing for both ears included the following:

- Air conduction thresholds as 125, 250, 500, 750, 1000, 1500, 2000, 3000, 4000, 6000, and 8000 Hz;
- Bone conduction thresholds at 12513, 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 Hz [14];

5.1.7. Subgroup Analyses and Pooling Results across Sites

The consistency of the primary endpoints was examined across subgroups of subjects defined by the following baseline characteristics: gender, race, duration of severe-to-profound hearing loss, and baseline CNC scores. Similarly, the consistency of the primary endpoints was examined across investigational sites by testing for an effect of site in an ANOVA model. Potential variation between sites in the primary endpoints was explored.

Of particular interest was the effect of a decrease of low frequency hearing, postoperatively. To examine this effect, analyses were performed on the primary endpoint (6 months postactivation) speech perception measures separately for subjects with varying degrees of levels of low frequency hearing loss; i.e. mild (26 through 40 dB HL), moderate (41 through 55 dB HL), moderate-severe (56 through 70 dB HL), severe (71 through 90 dB HL), profound (91+ dB HL), or total (no measurable hearing). Based on the outcomes of these analyses they were condensed into two subgroups based on postoperative hearing status:

- Group 1: Severe or better (moderate, moderately-severe, and severe),
- Group 2: Profound (profound and total).

Subanalyses were then conducted by group on outcomes for efficacy, music and self-assessment.

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[13] Bone conduction measures at 125 Hz were optional based on potential audiometric equipment limitations.
[14] Many audiometers are not calibrated for testing at 6000 and 8000 Hz.

Exploratory analyses were also performed to determine if there were any factors predictive of postoperative low frequency hearing loss, including duration of hearing loss, gender, and age.

5.1.8. Adverse Events

Adverse events were reported to the Sponsor via the Adverse Event form provided to each center. Adverse events were reported if observed, even if acknowledged as risk factors in the consent. These risk factors included:

- Sudden changes in residual low frequency hearing,
- Total loss of residual hearing,
- Vertigo, dizziness, or balance problems that did not exist preoperatively or worsened postoperatively,
- Facial nerve problems,
- Meningitis,
- Perilymphatic fistulae,
- Tinnitus that did not exist preoperatively or worsened postoperatively,
- Implant migration/extrusion,
- Skin flap problems,
- Device related/programming problems.

All adverse events were tabulated for 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). This was compared qualitatively to previous cochlear implant studies. Time to first adverse event was summarized using Kaplan-Meier plots. Exploratory proportional hazards regression models were used to determine whether baseline factors were associated with risk for adverse events over the course of the study. Hazard ratios and 95% confidence intervals for these analyses were cited.

Individual audiometric data were examined across test intervals to assess any changes in hearing sensitivity and to characterize the impact of the procedure on residual hearing sensitivity in the low frequencies.

6. PIVOTAL STUDY RESULTS

The results discussed herein reflect outcomes based on database closure for Premarket Submission (PMA) as of May 31, 2013.

6.1. Enrollment and Accountability of PMA Cohort

One hundred subjects were consented to be evaluated for participation in the clinical study; 50 were enrolled and implanted at 10 investigative sites.

Of the 50 subjects implanted:

- All had devices activated and completed the 3 month postactivation test interval.
- Forty-nine subjects completed the 6 month evaluation (primary endpoint):
    - One subject [redacted]) was reimplanted with a cochlear implant due to poor performance and loss of hearing sensitivity and did not complete the 6 month test interval.
- Of the 49 subjects completing the 6 month evaluation, 46 subjects completed the 12 month evaluation:
    - Two subjects [redacted] and [redacted] withdrew from the study prior to the 12 month test interval because they were diagnosed with serious medical conditions unrelated to the device or procedure.
    - One subject ([redacted] was reimplanted with a cochlear implant due to poor performance and loss of hearing sensitivity and did not complete the 12 month interval.

Table 3 is provided as a reference to account for differences in the number of subjects with data available for the various analyses described below. The table provides further information as to the test measures completed for the study group across the 12-months during which speech perception, hearing sensitivity, and self-assessment and other measures were made.

Table 3: Number of subjects completing study test measures as a function of pre- and postactivation interval. Note that subscripted values in the table are explained below.

	Preoperative	3 Month Interval[1]	6 Month Interval[2]	12 Month Interval[3]
Speech Perception Measures	N=50	N=50	N=49	N=46
Hearing Sensitivity measures	N=50	N=50	N=48[2a]	N=46
Self-Assessment and Other Measures				
DUQ	N=50	N/A	N=48[2a]	N=46
SSQ	N=50	N/A	N=48[2a]	N=46
UW-CAMP	N=50	N/A	N=47[2ab]	N/A

1. All implanted subjects completed the pre-implant and 3 month interval testing. Note that self-assessment and other measures were not assessed at 3 months.
2. By the 6 month interval, one subject was reimplanted ([redacted] and did not complete any testing at 6 and 12 months postactivation.
    a. An additional subject completed speech perception measures only at the 6 month interval [redacted].
    b. Subject [redacted] did not complete the UW-CAMP, but did complete the other measures.
3. By the 12 month interval a total of 2 subjects had been reimplanted ([redacted] and [redacted]. Two additional subjects withdrew from the study due to non-study related medical issues ([redacted] leaving an N of 46.

For primary endpoint measures at 6 months postactivation, 49 subjects had data available for speech perception measures and 48 subjects had hearing sensitivity data available for analysis. Therefore, when data is described relating speech perception outcomes and hearing sensitivity outcomes 48 subjects presented with data for both outcome measures.

6.2. Study Population Demographics

Of the 50 implanted subjects, 50% (25) were men, and 50% (25) were women. At the time of implantation, the average age of the subjects was 64.1 years (14.7 SD). Key demographics of the study population are shown in Table 4.

Table 4: Demographics for the 50 study subjects.

Demographic Characteristics	Mean ± SD N (min, max)
Age at CI in Years	64.1 ± 14.7 50 (23.0 – 86.2)
Duration of Overall Hearing Loss in Years	28.1 ± 14.9 50 (3.4 – 73.9)
Duration of High Frequency Hearing Loss in Years	13.1 ± 7.2 50 (1.6 – 30.1*)
Male	25/50 (50.0%)
Female	25/50 (50.0%)
Onset of Hearing Loss:	
Sudden	1/50 (2.0%)
Gradual	49/50 (98%)
Preoperative Hearing Aid Use:	
Bilateral Hearing Aids	38/50 (76%)
Unilateral Hearing Aid	9/50 (18%)
No Hearing Aids	3/50 (6%)
Cause of Hearing Loss:	
Unknown	25/50 (50.0%)
Noise Exposure	11/50 (22.0%)
Familial	9/50 (18.0%)
Autoimmune	1/50 (2.0%)
Familial/Otosclerosis	1/50 (2.0%)
Fever	1/50 (2.0%)
Noise Exposure/Viral	1/50 (2.0%)
Ototoxic Drugs	1/50 (2.0%)
Preoperative Degree of LF PTA (Implanted Ear):	
Normal (0 – 25 dB HL)	1/50 (2.0%)
Mild (26 - 40 dB HL)	13/50 (26.0%)
Moderate (41 – 55 dB HL)	26/50 (52.0%)
Moderate-Severe (56 – 70 dB HL)	10/50 (20.0%)

* One subject met the requirement of < 30 years duration of severe to profound high frequency loss at candidacy assessment but was slightly over 30 years duration by the time surgery was approved for reimbursement and completed.

6.3. Enrollment by Site and Site Effects

Table 5 provides the number of surgeries completed by study site and primary investigator. New York University was the lead investigational study site, completing 10 of the 50 surgeries.

Table 5: Investigational sites, Primary Investigators and number of surgeries completed.

Site ID	Investigational Site	Primary Investigator	Number of Surgeries
1003	New York University Medical Center (Lead)	J. Thomas Roland, M.D.	10
1050	Midwest Ear Institute	Charles Luetje, M.D.	11
0029	Hearts for Hearing	Stanley Baker, M.D.	6
1131	Mayo Clinic	Colin Driscoll, M.D.	7
1339	Northwestern University	Alan Micco, M.D.	3
1059	Ohio State University	Bradley Welling, M.D.	3
1523	Rocky Mountain Ear Center	David C. Kelsall, M.D.	3
1168	University of Cincinnati	Ravi Samy, M.D.	3
1001	University of Iowa	Bruce Gantz, M.D.	3
1411	Center for Hearing & Balance	Jacques Herzog, M.D.	1

The consistency of the primary endpoints was examined across investigational sites by testing for an effect of site in an ANOVA model. A site effect associated with a p-value less than 0.10 was considered evidence of possible variation between sites. Results of this analysis indicated no effect of site on mean benefit scores (6 month endpoint scores minus preoperative aided scores) observed for both the CNC ($p = 0.42$) and AzBio ($p = 0.63$) tests in the treated-ear condition.

Figure 14 shows the mean pre- and 6 month postactivation scores for each site for the CNC and AzBio tests. Although absolute scores vary somewhat site to site, all sites demonstrated significant improvement in mean scores (except AzBio sentences in noise for site 1411 who implanted one subject).

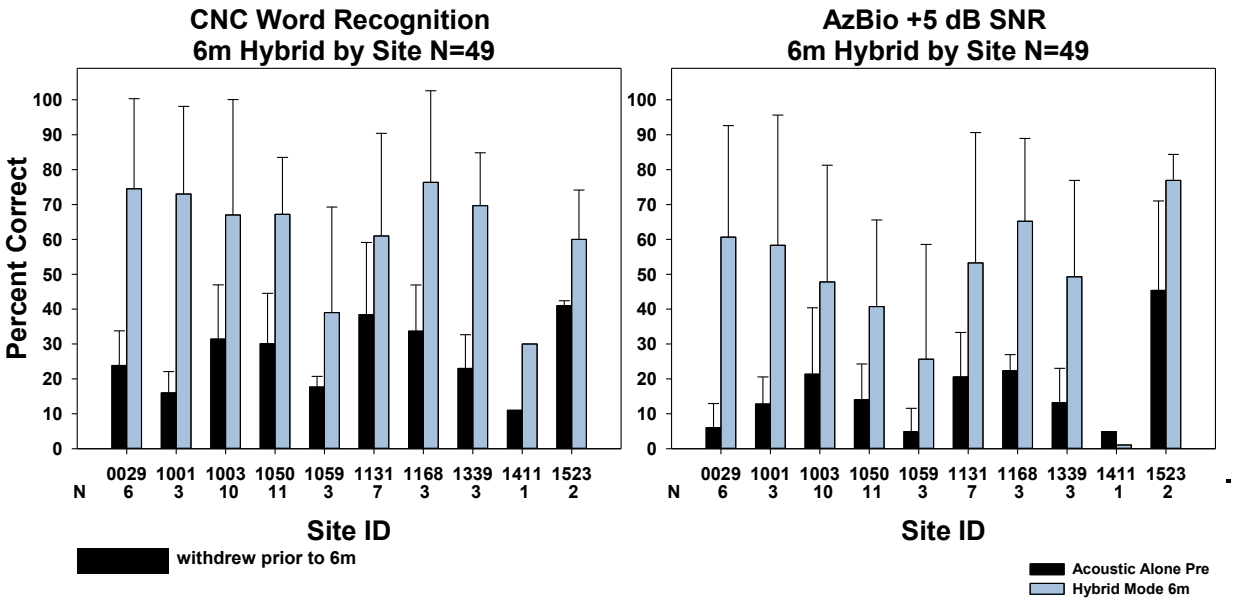

Figure 14: Mean pre- and postoperative CNC and AzBio sentences-in-noise scores for the implanted ear by site.

6.4. Effectiveness

6.4.1. Primary Endpoint Analyses - Speech recognition at 6 months postactivation

The co-primary efficacy endpoints for this study were the assessment of the within-subject mean differences in CNC words and AzBio sentences-in-noise measured in the implanted ear at 6 months postactivation (in Hybrid Mode[15]) compared with the preoperative assessment (Acoustic Alone). Figure 15 shows the mean pre- and 6 month postactivation scores for the CNC and AzBio tests. For reference, horizontal bars are drawn representing the mean scores observed for traditional cochlear implant users. In the case of the CNC test, the mean score observed in a clinical trial of the Freedom Cochlear Implant System was 52% at 6 months postactivation. The mean score observed for the Hybrid study subjects was 65%, almost 15 percentage points higher. In the case of the AzBio in noise test (at +5 dB SNR) the mean score for all Hybrid subjects tested at 6 months (49%) was almost twice that observed, 27%, for "typical" cochlear implant

[15] Note that in cases where subjects did not use the acoustic component scores obtained with Electric Stimulation alone were used.

users[16]. These comparisons underscore the significant benefit to be derived by combining electric and acoustic hearing in individuals who have significant high frequency sensorineural hearing loss.

As shown in Table 6 significant improvement was noted for both test measures. On average, in Hybrid Mode, subjects experienced a mean significant improvement of 37 percentage points (range = -41 to 79 percentage points) for CNC word recognition ($p < 0.0001$) and a mean 32.8 percentage points (range = -13.6 to 91.5 percentage points) improvement for AzBio sentences in noise ($p < 0.0001$).

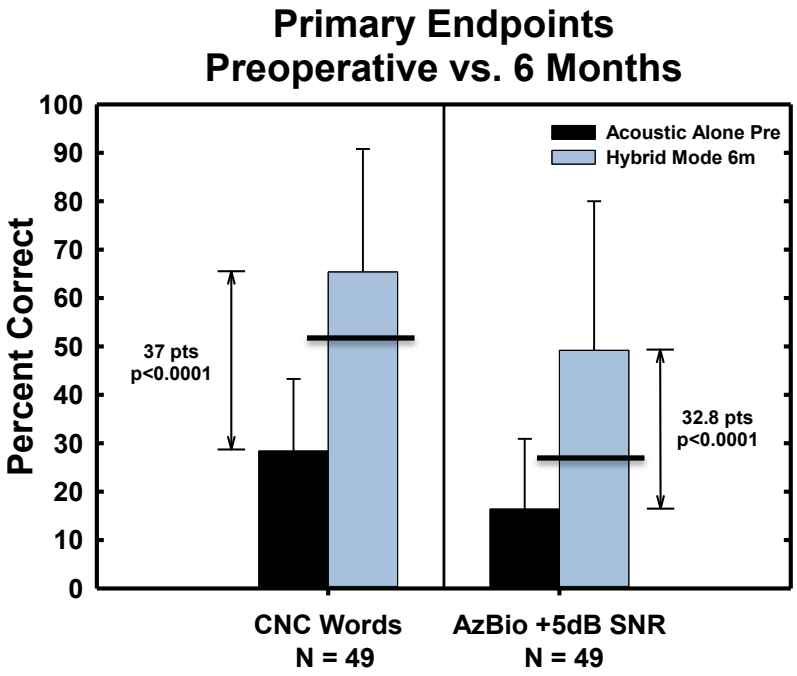

Figure 15: Mean pre- and postoperative outcomes for CNC word recognition and AzBio in noise (+5 dB SNR) tests for the Hybrid Mode. Horizontal bar on the left indicates the mean CNC score at 6 months from the Freedom clinical trial (N=53). Horizontal bar to the right indicates the mean score for the "typical" implant user (Dorman & Spahr, 2006).

[16] Dorman, M.F. & Spahr, A.J. (2006) Speech Perception by Adults with Multichannel Cochlear Implants in S.B. Waltzman, S.B. & Roland, J.T. Eds. Cochlear Implants, 2nd. Edition, Thieme, NY, Stuttgart.

Table 6: Primary efficacy endpoints met; statistical summary.

(N=49)#	Acoustic Alone Preoperative	Hybrid Mode 6 Months Postactivation	Percentage Point Change	P-Value*
	Mean ± S.D.	Mean ± S.D.	Mean ± S.D. (95% C.I)	
Word Scores	28.4% ± 14.7%	65.4% ± 25.4%	37.0 ± 26.6 (29.4, 44.6)	p < 0.0001
AzBio Scores	16.3% ± 14.4%	49.2% ± 30.8%	32.8 ± 29.1 (24.5, 41.2)	p < 0.0001

* Student's t-test p-value; signed-rank p-value if normality assumption failed.
# Subject [redacted] was reimplanted prior to the 6 month interval and was not included in the analyses, but is included in the mean scores preoperatively (N=50).

These analyses support that both primary endpoints, were met for this clinical study, namely:

- The mean score obtained by the subjects using the Hybrid L24 Implant System in the Hybrid Mode was significantly improved over that obtained Acoustic Alone, preoperatively, for CNC word recognition and,
- The mean score obtained by the subjects using the Hybrid L24 Implant System in the Hybrid Mode was significantly improved over that obtained Acoustic Alone, preoperatively, for AzBio sentence recognition in noise.

6.4.2. Bilateral Outcomes

As described above co-primary efficacy endpoints for this study were based on measures made for the implanted ear alone at 6 months postactivation compared with the preoperative Acoustic Alone condition. However, it is important to recognize that subjects made use of bilateral hearing on an everyday basis. That is, they used the Hybrid L24 device in concert with hearing, typically aided, in the contralateral ear (i.e., Combined Mode[17]). The Combined Mode is very important as it most reflects

[17] Note that in cases where subjects did not use the acoustic component scores obtained with the Bimodal Mode were used.

performance in the condition used by subjects in their daily lives, just as bilateral hearing aids reflected the listening condition of most subjects prior to implantation. Figure 16 shows the mean pre- and 6 month postactivation CNC and AzBio sentences in noise scores for the bilateral condition.

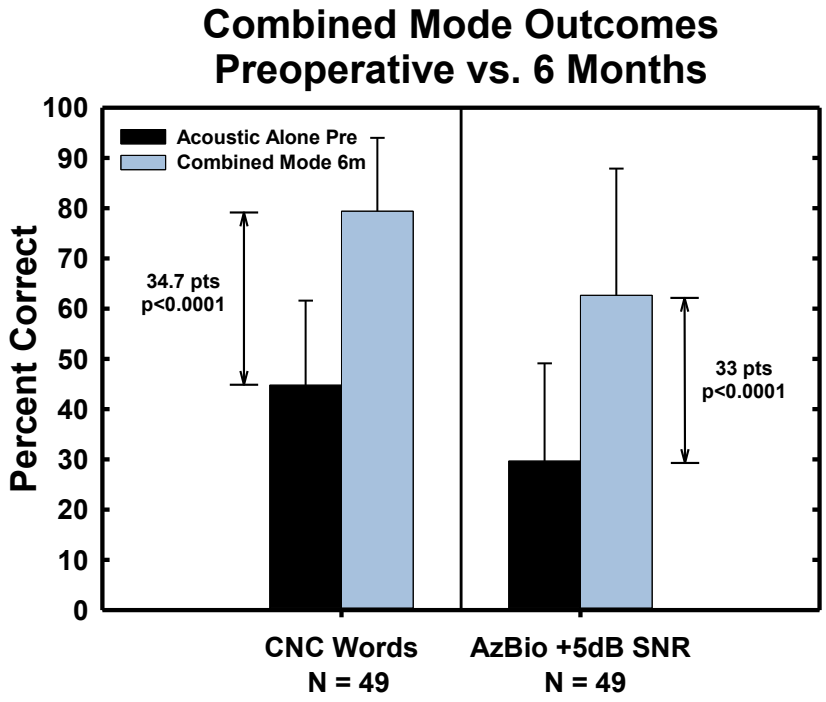

Figure 16: Mean Pre- and Postoperative outcomes for the CNC Word Recognition and AzBio in Noise (+5 dB SNR) Tests for the Combined Mode.

As shown in Table 7 significant improvement was noted for both test measures. On average, in the Combined Mode, subjects experienced a mean significant improvement of 34.7 percentage points (range = 1 to 72 percentage points) for CNC word recognition ($p < 0.0001$) and a mean 33.0 percentage points (range = -1.9 to 85.1 percentage points) improvement for AzBio sentences in noise ($p < 0.0001$).

These analyses further support that the Hybrid L24 implant significantly improved hearing for speech perception, namely:

- The mean score obtained by the subjects using the Hybrid L24 Implant System in the Combined Mode was significantly improved over that obtained with appropriately fit bilateral hearing aids (Bilateral Acoustic Mode), preoperatively, for CNC word recognition and,
- The mean score obtained by the subjects using the Hybrid L24 Implant System in the Combined Mode was significantly improved over that obtained with

appropriately fit bilateral hearing aids (Bilateral Acoustic Mode), preoperatively, for AzBio sentence recognition in noise.

Table 7: Combined Mode; statistical summary.

(N=49)#	Bilateral Acoustic Preoperative	Combined Mode 6 Months Postactivation	Percentage Point Change	P-Value*
	Mean ± S.D.	Mean ± S.D.	Mean ± S.D. (95% C.I)	
Word Scores	44.9% ± 16.1%	79.4% ± 14.6%	34.7 ± 17.4 (29.7, 39.7)	p < 0.0001
AzBio Scores	29.6% ± 19.3%	62.6% ± 25.3%	33.0 ± 23.5 (26.2, 39.7)	p < 0.0001

* Student's t-test p-value; signed-rank p-value if normality assumption failed.
# Subject [redacted] was reimplanted prior to the 6 month interval and was not included in the analyses, but is included in the mean scores preoperatively (N=50).

6.4.3. Secondary Endpoint Analyses

Secondary efficacy endpoint analyses were based on binomial comparisons of pre- and postoperative speech scores for the CNC test, scored for both words and phonemes correct, and the AzBio test in noise.

As shown in Table 8, the secondary endpoints (> 75% of subjects performing *equal to or better than* the preoperative Acoustic Alone Mode) were met and exceeded for both metrics (Hybrid Mode).

Table 8: Proportion of subjects with postoperative score equal to or better than preoperative at 6 Month study interval.

Listening Mode N=49	CNC Words	CNC Phonemes	AzBio in Noise
Hybrid (Study Endpoint)	98.0%	91.8%	89.8%
Combined (Everyday Use)	100%	100%	100%

It is important to consider that in the Combined Mode no subject showed a significant decrement pre- to postoperatively. In other words, 100% of the subjects performed equal to or better than they did preoperatively with appropriately fitted bilateral hearing aids

(Bilateral Acoustic) when tested in the Combined Mode (i.e., both ears acoustically in addition to the Hybrid cochlear implant) at the 6 month endpoint.

Although not pre-specified in the study protocol for endpoint analyses, it was of interest to examine what proportion of the subjects showed significant improvements based on binomial comparisons. Table 9 provides a similar summary of the data as Table 7 except that only those scores found to be significantly better than the preoperative condition are considered. Under this scenario most (> 75%) subjects scored significantly better than they did preoperatively for all measures, except AzBio sentences in noise for the Hybrid condition where 73.5% of the subjects scored significantly better than preoperatively based on binomial comparisons.

Table 9: Proportion of subjects with postoperative score better than preoperative at 6 Month study interval.

Listening Mode N=49	CNC Words	CNC Phonemes	AzBio in Noise
Hybrid (Study Endpoint)	81.6%	85.7%	73.5%
Combined (Everyday Use)	87.8%	89.9%	83.7%

6.4.4. Other Assessments for Efficacy

6.4.4.1. The University of Washington Clinical Assessment of Music Perception (UW-CAMP)

The University of Washington Clinical Assessment of Music Perception (UW-CAMP) music test battery was used to assess music perception abilities. The UW-CAMP consists of three subtests (pitch discrimination, melody recognition and perception of timbre). The UW-CAMP was administered in the Acoustic Alone, Bilateral Acoustic, Hybrid, and Combined Modes.

It is generally accepted that cochlear implantation delivers the potential for significantly improved speech perception but music perception/appreciation remains relatively poor via electric stimulation (Kang et al., 2009). A potential benefit of E+A stimulation is an improvement in music perception/appreciation for Hybrid recipients as compared to conventional cochlear implant recipients and/or no decrement in outcomes as compared to the preoperative hearing aid condition. Results are presented for the Hybrid L24 study population compared with a normal hearing cohort (Kang et al., 2009) across the three subtests.

6.4.4.1.1. Pitch Discrimination Subtest

Mean scores for the Hybrid subjects are contrasted with normally hearing individuals in Figure 17. As shown, normally hearing individuals can discriminate tones that are 1 semitone apart on average, as measured by this test. Hybrid subjects (to the right) performed at levels similar to that observed for the normally hearing subjects. In summary, the Hybrid subjects maintained their pitch discrimination abilities pre- to postoperatively for the treated ear (Acoustic Alone vs. Hybrid Mode).

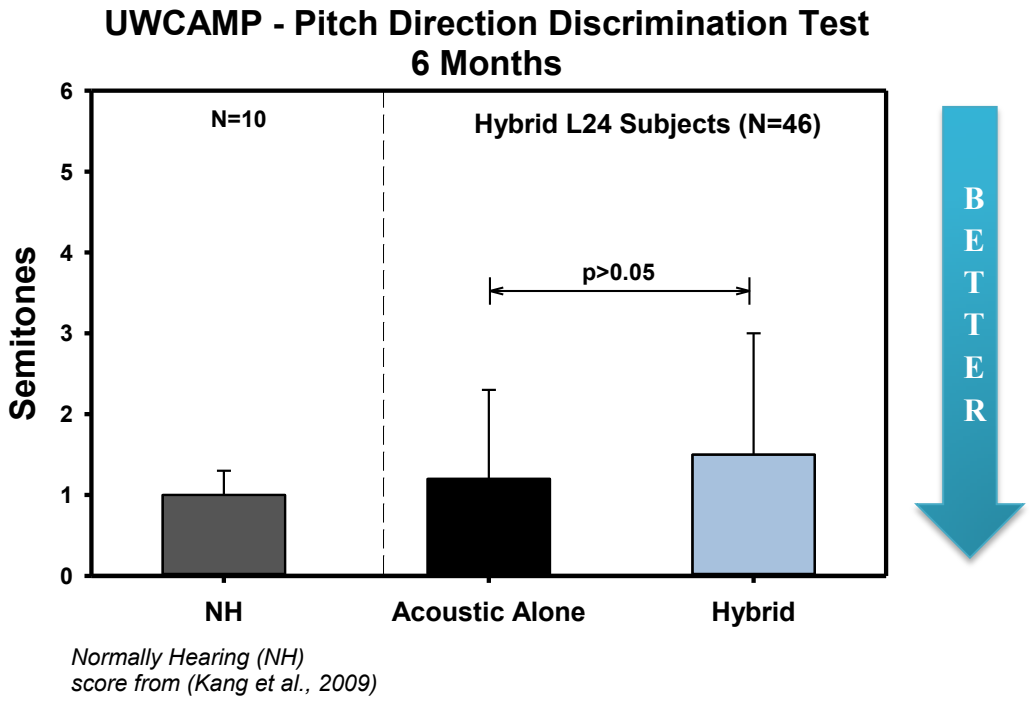

Figure 17: UW-CAMP mean pitch discrimination thresholds for normal hearers and Hybrid L24 subjects.

6.4.4.1.2. Melody Recognition Subtest

Normally hearing individuals correctly recognized familiar melodies with a mean score of 87.5%, as shown in Figure 18 for 47[18] subjects with pre- and postoperative data. Hybrid users performed at a level somewhat poorer than that observed for the normal hearing subjects but, importantly, they maintained their melody recognition abilities pre- to postoperatively for the treated ear (Acoustic Alone vs. Hybrid Mode).

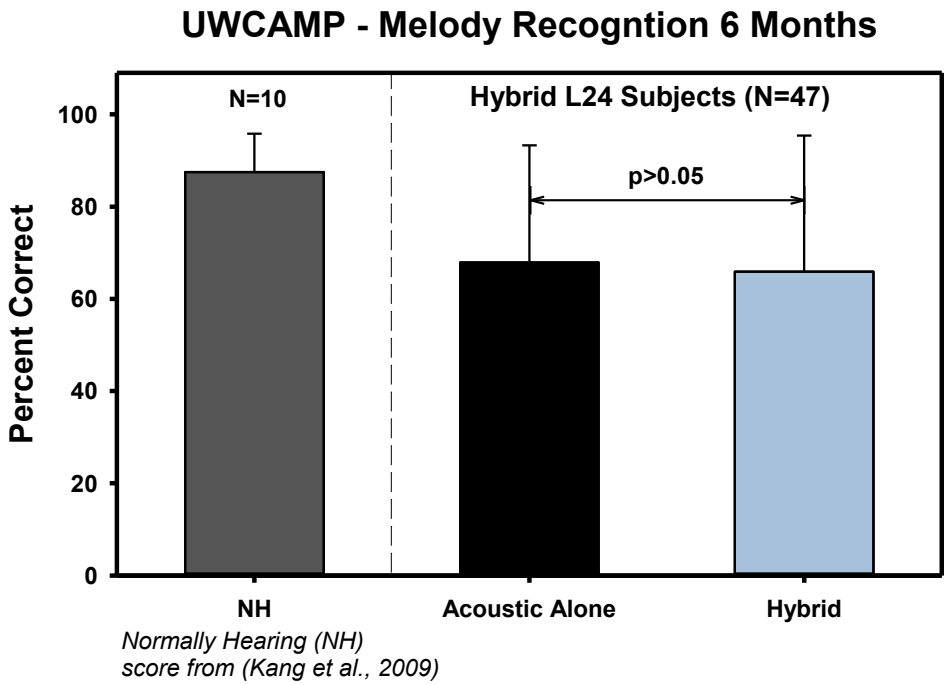

Figure 18: UW-CAMP mean melody recognition for normal hearers and Hybrid L24 subjects.

[18] One subject was not assessed as he/she did not understand the task (and was subsequently diagnosed with advancing dementia), a second subject did not complete the test due to time constraints, and a third subject was reimplanted prior to the 6-month test interval.

6.4.4.1.3. Timbre Recognition Subtest

Normally hearing individuals correctly recognized timbre with a mean score of 94.2%, as shown in Figure 19 (Kang et al., 2009). Similarly to the Melody Recognition subtest, the Hybrid subjects maintained their timbre recognition abilities pre- to postoperatively for the treated ear (Acoustic Alone vs. Hybrid Mode).

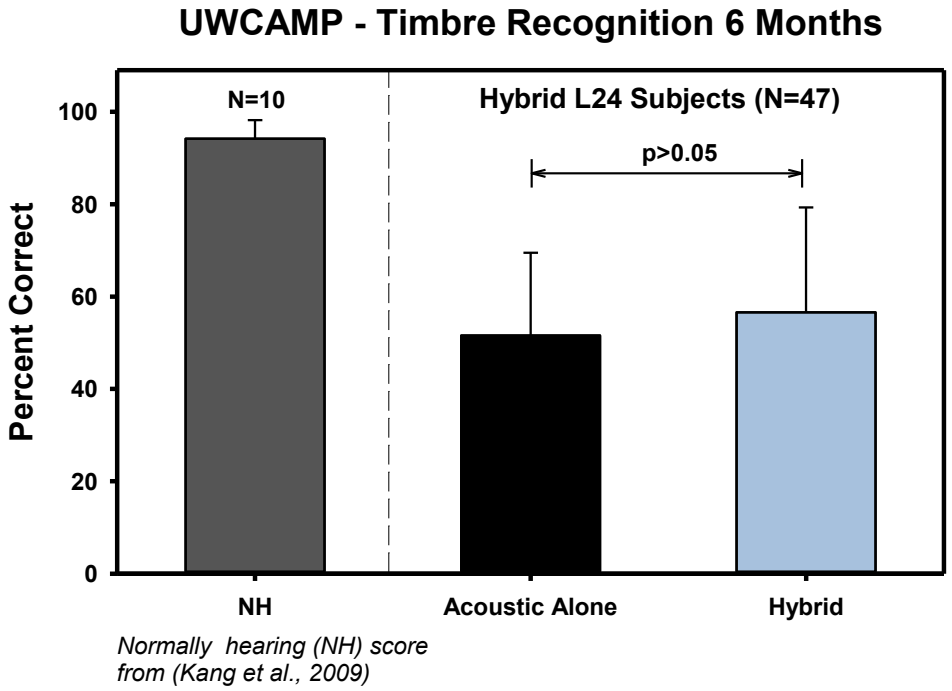

Figure 19: UW-CAMP mean timbre recognition for normal hearers and Hybrid L24 subjects.

6.4.4.2. Self-Assessment Questionnaires

6.4.4.2.1. Speech, Spatial, and Qualities of Sound Questionnaire

The Speech, Spatial and Qualities of Hearing Scale (SSQ) measured listening ability in a large number of listening situations categorized into three domains. Fifty subjects completed the SSQ preoperatively, and 48 completed it at 6 months postactivation[19].

[19] 12 month data not discussed in this report.

Comparisons were made between the preoperative and postoperative bilateral conditions[20] as this is the condition used in daily life. Results are graphically represented in Figure 20.

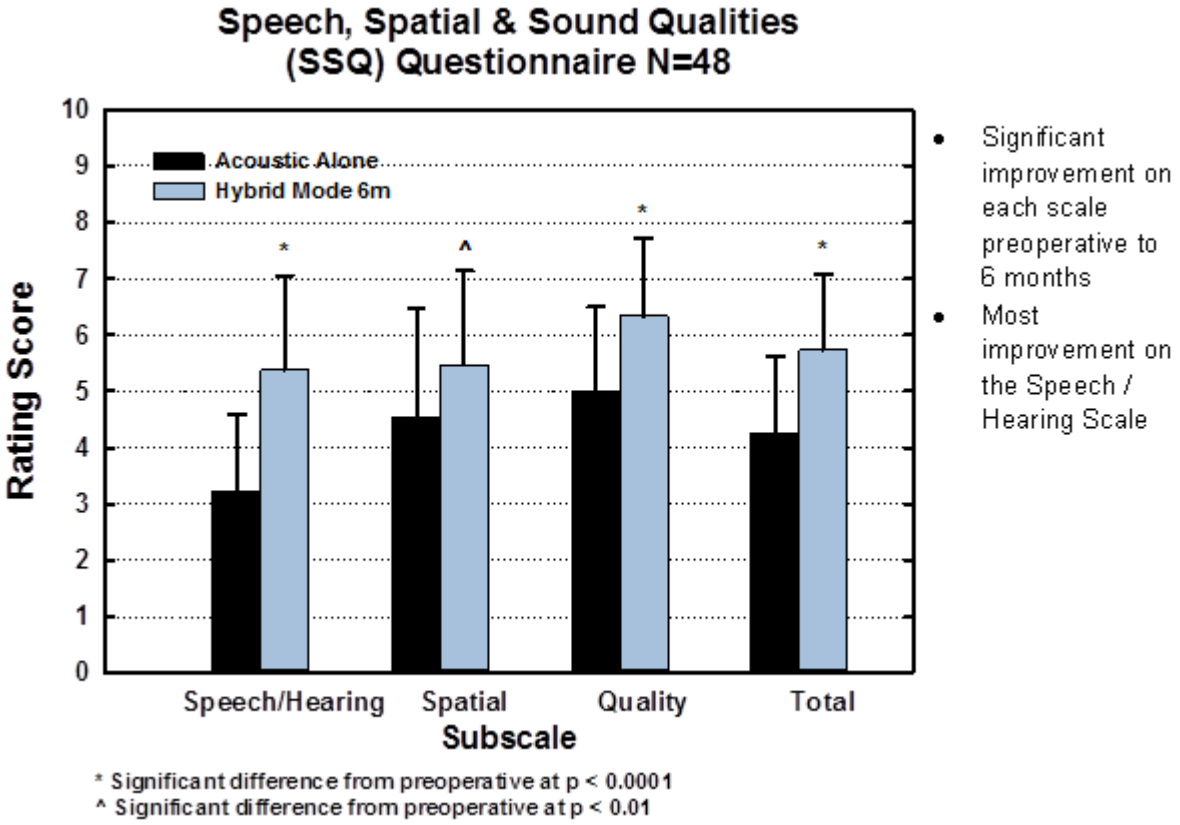

Figure 20: Mean SSQ outcomes for three hearing domains and total ratings.

Individual comparisons preoperative to 6 months were analyzed for each scale and the total SSQ score using the category scheme described by Noble et al. (2009). The scheme was as follows:

- Negative Benefit: ≤ -1 point change;
- No Change: a change < 1;
- Benefit/Very High Benefit: > 1 point positive change.

[20] For most subjects this corresponded to the Combined Mode postoperatively. For subjects who had profound or total loss of hearing and ceased using acoustic amplification in the implanted ear, the Bimodal Mode was the postoperative comparison.

Based on this approach, the 48 Hybrid subjects reported responses yielding the following results shown in Table 10:

Table 10: SSQ outcomes based on category scheme of Noble et al. (2009).

Scale	Negative	No Change	Benefit/High Benefit
Speech	6%	17%	77%
Spatial	19%	27%	54%
Qualities	10%	31%	59%
Total Score	15%	19%	66%

The overall subjective findings of the SSQ on a group and individual subject basis appear to support improved hearing performance with the Hybrid L24 as evaluated on the objective speech perception test measures that assessed hearing for speech both in quiet (CNC words) and in noise (AzBio Sentences).

6.4.4.2.2. Device Use Questionnaire (DUQ)

While the SSQ addressed self-perceived benefit for hearing in various everyday listening situations, unlike the DUQ, it did not address questions concerning acclimatization, device manipulation, preferred listening modes in a variety of listening conditions, as well as overall satisfaction. For example, the DUQ included questions concerning preferred device listening modality (i.e., Hybrid Mode, Combined Mode, Bimodal Mode etc.) across various listening conditions (e.g., using the telephone, noisy environments, groups, music and others).

Fifty subjects completed the DUQ preoperatively, and 48[21] completed the DUQ at 6 months postactivation.

Preoperatively, 100% (50/50) of the subjects utilized some form of acoustic hearing bilaterally. For the purposes of the study, appropriately fit bilateral hearings aids were required. If a subject did not use amplification bilaterally a minimum 14-day trial period

[21] The 48 subjects were the same 48 subjects that completed the DUQ, MBQ, and SSQ at the 6 month interval.

was required[22]. For this questionnaire, the subjects reported preoperative device use preferences as follows:

- 76% (38/50) of the subjects used bilateral hearing aids as the preferred mode of listening,
- 14% (9/50) used only one hearing aid, and
- 6% (3/50) used no hearing aids.

The following was also reported:

- 76% (38/50) reported being "very dissatisfied" or "dissatisfied" with their overall preferred way of listening (for 47/50 with hearing aids),
- 16% (8/50) reported being "neutral", and
- 8% (4/50) reported being "satisfied or very satisfied".

At the 6 month endpoint, 65% (31/48) preferred listening bilaterally, with or without amplification, in addition to electric hearing via the Hybrid L24 implant), while 29% (14/48) preferred to use the Hybrid L24 implant with a hearing aid in the other ear only. Six percent (3/48) subjects preferred the Hybrid Mode; however, these subjects also had useful acoustic hearing in the contralateral ear without amplification so in effect were using hearing in both ears.

The DUQ included more than 90 questions, which will not be summarized here for the sake of brevity. However, as an example, Figure 21 compares preoperative and 6 month postactivation responses to the following question: "Using your preferred way of listening, please rate your level of satisfaction for understanding speech in each of the following situations."

Red sections of the bars in Figure 21 indicate the number of subjects (N=50 preoperative, N=48 postoperative) who were "Very Dissatisfied" or "Dissatisfied" for the various listening situations, orange sections indicate the number who reported being "Neutral," green shows those who were "Very Satisfied" or "Satisfied," with grey indicating those who answered "Does Not Apply." In general, the red sections are longer preoperatively across all listening situations, indicating that the larger proportion of subjects were dissatisfied with their performance using amplification preoperatively. Postoperatively,

[22] One subject with recent bilateral hearing aid experience was permitted to undergo a 10-day trial for preoperative assessment.

the red sections are shorter, with the green sections longer, indicating that many subjects migrate from feeling dissatisfied to satisfied with their hearing ability when using the Hybrid L24 Implant System. Across the situations summarized in Figure 19 the range of subjects indicating dissatisfaction preoperatively ranged from 22% (11/50) to 96% (48/50). In all situations the level of dissatisfaction decreased such the range was only 2% (1/48) to 40% (19/48), postoperatively. Conversely, levels of satisfaction preoperatively increased dramatically from a range of 0% to 44% (22/50) to 29% (14/48) to 94% (45/48), postoperatively. Situations that involved hearing in noise, at distance or in group situations presented the greatest levels of dissatisfaction for subjects. Even ratings for these situations improved pre- to postoperatively in all cases.

At 6 months postactivation, when asked about their level of satisfaction with overall performance with the Hybrid L24 system, 79% (38/48) reported being very satisfied or satisfied, 6% were neutral on the question, and only 15% (7/48) reported being dissatisfied. In terms of being satisfied with the decision to receive the Hybrid L24 81% (39/48) were very satisfied or satisfied, 10% (5/48) were neutral, and only 8% (4/48) dissatisfied.

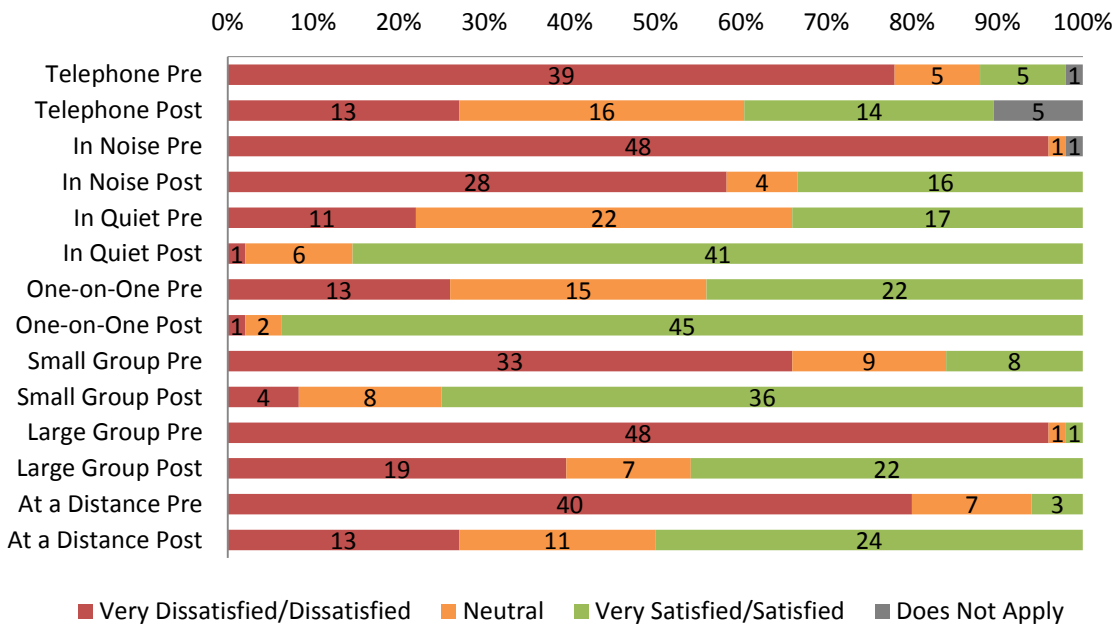

Figure 21: Level of satisfaction for understanding speech in various situations.

6.4.4.2.3. Musical Background Questionnaire

The Musical Background Questionnaire (MBQ) was originally developed by Gfeller et al. (2000) and adapted by the Sponsor for this study. It was administered at two intervals; preoperatively and 6 months postactivation. The MBQ probed musical training and experience before and after implantation. Although the MBQ provided a wealth of information regarding the music habits of the subjects, it was found not to be useful in terms of pre- to postoperative analyses.

6.5. Safety

The primary safety endpoint was defined as any surgical and/or device-related event, reported as the number and proportion of individuals experiencing the adverse event[23] across the duration of the study. Adverse events were reported even if acknowledged as risk factors in the informed consent.

Over the entire study period, 65 adverse events were observed (Table 11) involving 34 of the 50 Hybrid L24 subjects (i.e., some subjects had multiple events/symptoms). Fifty events were considered medical/surgical in nature and 15 device related (open and short circuited electrodes, sound quality issues, decrease in performance, and overstimulation). The medical/surgical events included instances of increased tinnitus, vertigo, and other symptoms typical of the mastoidectomy with facial recess approach used in cochlear implantation. The most common events observed related to profound or total loss of low frequency hearing and open/short circuited electrodes. Outside of the 22 cases of profound/total loss of hearing, all but two cases (one sound quality issue and one decrease in performance) were resolved as of database closure on May 31, 2013.

As this study involved implanting subjects with low frequency hearing unlike prior cochlear implant clinical trials, changes in hearing sensitivity were assessed and those that resulted in profound (> 90 dB HL) loss of low frequency hearing were also reported as anticipated adverse events.

[23] With corresponding 95% exact binomial confidence limits and the number of events per patient-time (e.g., events per 10 patient years).

Table 11: Number and percentage of adverse events observed for Hybrid L24 subjects.

Event	Number of Events	Percentage of Events	Number of Subjects with Event	Percentage of Subjects	Percentage Resolved
Profound/Total Loss	22	33.8%	22	44.0%	0.0%
Open/short circuited electrodes	11	16.9%	11	22.0%	100.0%
Increased tinnitus	6	9.2%	6	12.0%	100.0%
Tinnitus not present preoperatively	6	9.2%	6	12.0%	100.0%
Dizziness	3	4.6%	3	6.0%	100.0%
Dizziness with change in hearing	2	3.1%	2	4.0%	100.0%
Increased tinnitus with change in hearing	2	3.1%	2	4.0%	100.0%
Skin irritation due to externals	2	3.1%	2	4.0%	100.0%
Sound quality issue	2	3.1%	2	4.0%	50.0%
Decrease in performance	1	1.5%	1	2.0%	0.0%
Imbalance	1	1.5%	1	2.0%	100.0%
Imbalance with change in hearing	1	1.5%	1	2.0%	100.0%
Increased impedances with change in hearing	1	1.5%	1	2.0%	100.0%
Local stitch infection	1	1.5%	1	2.0%	100.0%
Overstimulation	1	1.5%	1	2.0%	100.0%
Pain in implant ear	1	1.5%	1	2.0%	100.0%
Vertiginous symptoms with change in hearing	1	1.5%	1	2.0%	100.0%
Vertigo	1	1.5%	1	2.0%	100.0%
Total	**65**				

Kaplan-Meier curves were generated separately for all adverse events observed, adverse events related to profound/total loss of hearing, and for non-hearing related events (Figure 22). The adverse events observed during the study tended to occur within the first 6 to 8 months of device use post-surgery.

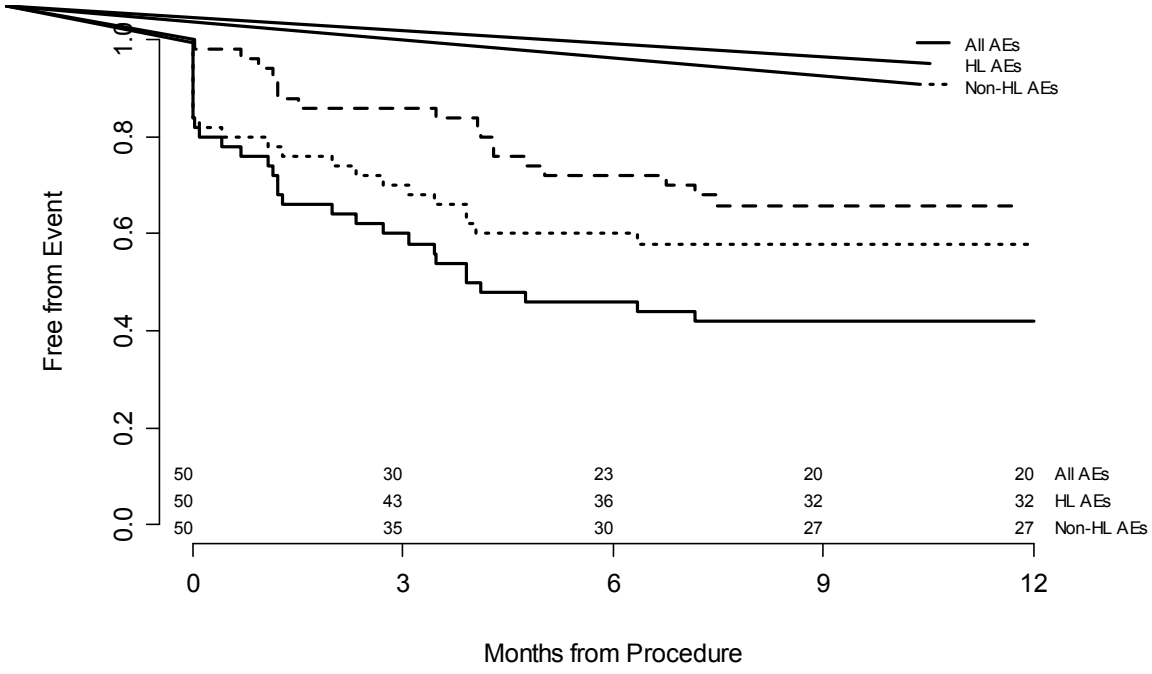

Figure 22: Kaplan-Meier curves showing freedom from all adverse events (solid line), non-hearing related adverse events (dotted line), and profound/total loss of hearing (dashed line).

The association of baseline characteristics with adverse events and profound/total loss of hearing was examined using univariate Cox proportional hazards regression models (for all adverse events including profound/total loss of hearing and for profound/total loss of hearing separately), the results of which are provided in Table 12 and Table 13. The baseline characteristics evaluated included age at implantation, duration of hearing loss, duration of severe-profound hearing loss, etiology, and preoperative speech perception outcomes. Of the baseline factors examined, none were found to be significantly associated with either outcome of adverse event or profound/total loss of hearing (all p-values > 0.05).

Table 12: Univariate Cox proportional hazards regression models for all adverse events including profound/total loss of hearing.

Covariate	Hazard Ratio [95% CI]	P-value
Age	1.01 [0.99, 1.04]	0.3828
Duration of Hearing Loss	1.01 [0.99, 1.04]	0.2495
Duration of Severe-Profound HF Hearing Loss	0.98 [0.94, 1.03]	0.5172
Etiology	NA*	0.6633
Preoperative CNC Word-Acoustic Alone	1.00 [0.98, 1.03]	0.8479
Preoperative CNC Word-Bilateral Acoustic	1.01 [0.99, 1.03]	0.1825
Preoperative AzBio Sentence-In-Noise	1.01 [0.99, 1.03]	0.1825
Preoperative AzBio Bilateral Acoustic	1.00 [0.99, 1.02]	0.7001
Results reported from Cox proportional hazards model. * Type III P-value displayed. Because the covariate is multi-level and categorical so single hazard ratio estimate can be obtained.		

Table 13: Univariate Cox proportional hazards regression models profound/total loss of hearing.

Covariate	Hazard Ratio [95% CI]	P-value
Age	1.02 [0.99, 1.05]	0.2211
Duration of Hearing Loss	1.01 [0.99, 1.04]	0.4245
Duration of Severe-Profound HF Hearing Loss	1.00 [0.94, 1.06]	0.9510
Etiology	NA*	0.9996
Preoperative CNC Word-Acoustic Alone	1.00 [0.98, 1.03]	0.7854
Preoperative CNC Word-Bilateral Acoustic	1.01 [0.99, 1.04]	0.3218
Preoperative AzBio Sentence-In-Noise	1.01 [0.99, 1.04]	0.3218
Preoperative AzBio Bilateral Acoustic	1.01 [0.99, 1.03]	0.4069
Results reported from Cox proportional hazards model. * Type III P-value displayed. Because the covariate is multi-level and categorical so single hazard ratio estimate can be obtained.		

Data regarding the frequency and severity of peri- and postoperative surgical complications was also compared to the results of a previous cochlear implant study. Table 14 contains an adverse event summary for both the Hybrid L24 pivotal study and the most recent cochlear implant study[24]. The data reported in this table was based on database closure for the Hybrid L24 study as of May 31, 2013 and closure of the Freedom study as of August 31, 2007. If a particular adverse event was not reported or was not applicable across both studies, it was identified by 'N/A' in the table. Overall, the events reported (outside of those related to loss of hearing) were similar in type and severity to those observed in the Freedom trial, with the main differences being the number of open/short circuited electrodes and new tinnitus cases reported. With respect to open and short electrodes, it should be noted that in the Freedom trial, data were only collected for five electrodes across the array to monitor T and C levels in general. It is therefore likely that the number of overall occurrences was understated in this study.

[24] Nucleus Freedom, CI24RE.

Table 14: Adverse event summary for the Hybrid L24 (N=50) and Freedom (N=71) clinical trials.

Adverse Event	Number Occurring	
	Hybrid Subjects	Freedom Subjects
Profound/total loss of hearing	22¥	NA
Open/Short circuited electrodes	11	3
Increased tinnitus	6	8
Tinnitus not present preoperatively	6	2
Increased tinnitus with change in hearing	2	NA
Dizziness	3	4
Dizziness with change in hearing	2	NA
Imbalance	1	3
Increased imbalance	0	1
Imbalance with change in hearing	1	NA
Lightheadedness	0	1
"3D" vision/nausea	0	1
Vertigo	1	1
Increased vertigo	0	1
Vertigo with change in hearing	1	NA
Sound quality issues	2	0
Decreased performance	1	1
Increased impedances with change in hearing sensitivity	1	NA
Overstimulation	1	0
Taste Disturbance	0	1
Facial Paralysis/FNS	0	1
CSF Leak	0	1
Other	4†	2‡
¥ Included four subjects who elected to be reimplanted at a later date with a cochlear implant.		
† Other included 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.		
‡ Other included 1 report of skin reaction at incision site, 1 case of ingrown hair at incision site.		

6.6. Other Analyses

6.6.1. Acoustic Hearing Sensitivity Outcomes

A major element of this study was the opportunity for subjects to maintain a level of acoustic low frequency hearing that would allow use of electric + acoustic input in one ear with acoustic at the other. The preservation of low frequency hearing is possible after Hybrid L24 implantation as demonstrated in the clinical trial outcomes. This section will describe in detail the hearing sensitivity outcomes obtained during this trial and will also discuss the impact on overall hearing performance across the other test measures. Note that for terms of categorization and reporting of low frequency average thresholds, a five frequency pure tone average (PTA) was calculated over the following frequencies: 125 Hz, 250 Hz, 500 Hz, 750 Hz, and 1000 Hz.

Forty-eight[25] subjects had audiometric data available for the 6 month postactivation primary endpoint. Table 15 summarizes the low frequency pure-tone average categorized by degree of loss for the preoperative, initial activation, and the 3, 6, and 12 month intervals. As shown, at 6 months, 69%, of the subjects had a low frequency PTA in a moderate, moderate-severe or severe range. The remaining 31% (15/48) of subjects had low frequency PTAs in with the profound or total loss of hearing range. By the 12 month postactivation interval, 33/46 subjects (72%) retained severe or better levels of hearing, and 13/46 (28%) experienced profound/total loss, consistent with that observed at the 6 month interval.

[25] One subject [redacted]) evaluated at 3 months with a profound loss of hearing was not assessed audiometrically at 6 months but was assessed for efficacy. Another subject [redacted], also evaluated at 3 months with a profound loss of hearing, was reimplanted prior to the 6 month evaluation.

Table 15: Low frequency pure-tone average categorized by degree of loss at study intervals.

Degree of Low Frequency Hearing Loss (PTA 125-1k Hz)	Evaluation Interval				
	Preoperative	**Initial Activation**	**3 Months**	**6 Months**	**12 Months**
Normal (0 – 25 dB HL)	1 of 50 (2.0%)	--	--	--	--
Mild (26 – 40 dB HL)	13 of 50 (26.0%)	1 of 50 (2.0%)	--	--	--
Moderate (41 – 55 dB HL)	26 of 50 (52.0%)	15 of 50 (30.0%)	15 of 50 (30.0%)	15 of 48 (31.3%)	15 of 46 (32.6%)
Moderate - Severe (56 – 70 dB HL)	10 of 50 (20.0%)	18 of 50 (36.0%)	12 of 50 (24.0%)	9 of 48 (18.8%)	10 of 46 (21.7%)
Severe (71 – 90 dB HL)	--	10 of 50 (20.0%)	10 of 50 (20.0%)	9 of 48 (18.8%)	8 of 46 (17.4%)
Profound (> 90 dB HL)	--	5 of 50 (10.0%)	9 of 50 (18.0%)	10 of 48 (20.8%)	8 of 46 (17.4%)
Total (Nonmeasurable)	--	1 of 50 (2.0%)	4 of 50 (8.0%)	5 of 48 (10.4%)	5 of 46 (10.9%)

An alternate way of viewing the data is presented below in Figure 23. The height of each color at the study intervals represents the number of subjects in the corresponding hearing loss category, based on the low frequency pure tone average. Across study intervals, the greatest changes to the category of hearing are seen between the Preoperative and Initial Activation intervals. The number of subjects in each category at the 3, 6, and 12 month intervals are consistent across time intervals. This graphical representation shows that threshold shifts typically occur before the 3 month study interval and then remain relatively stable. This trend is also demonstrated in Section 6.6.2.

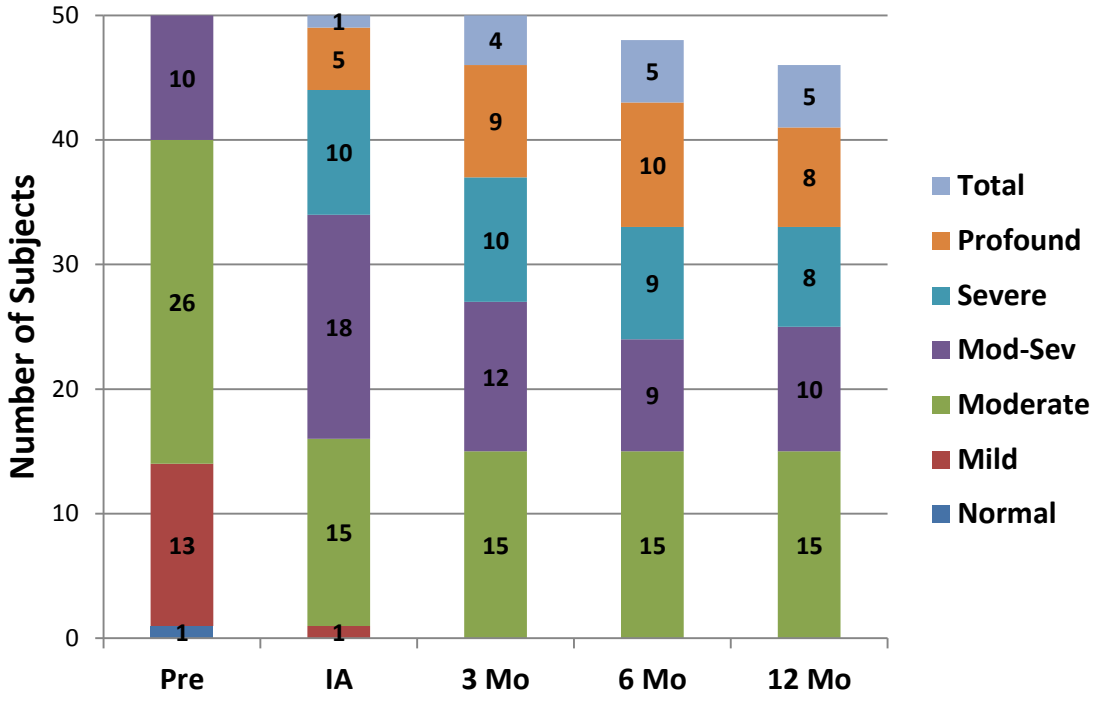

Figure 23: Low frequency pure-tone average viewed by degree of loss at study intervals

6.6.2. Average Threshold by Interval

Average low frequency pure-tone thresholds across the test intervals are shown in Table 16. So that hearing sensitivity outcomes for all 50 subjects were considered through 12 months, thresholds were imputed for subjects who did not complete 6 month audiometric testing (N=2 with profound/total loss) as well as 12 months (N=3 with profound/total loss and 1 with moderate loss). The data suggested that a decrease in hearing sensitivity will occur postimplantation. This risk was identified in the informed consent signed by all subjects. In 76% of the subjects, hearing thresholds shifted > 10 dB by 6 months postactivation.

When measured at the Initial Activation interval (4 weeks after surgery), the 50 subjects experienced a mean shift in the low-frequency PTA of 20.9 dB, relative to preoperative levels. By 3 months postactivation, a further change of 8.7 dB in hearing sensitivity was observed. Average thresholds beyond 3 months demonstrated relatively less change; from the 3 to 12 month interval, the low frequency PTA change was 4 dB.

Across frequencies, threshold shifts were relatively consistent. In other words, hearing sensitivity changes were relatively independent of frequency within the range 125

through 1000 Hz. Hearing thresholds appeared to stabilize by the 6 month test interval in a majority of the cases.

Table 16: Average thresholds across test interval.

Interval	125 Hz	250 Hz	500 Hz	750 Hz	1000 Hz	Low Frequency PTA
Preoperative N=50	26.6	28.5	41.7	58.1	71.6	45.3
Initial Activation N=50	46.8	48.3	63.5	79.3	92.9	66.2
3 Month N=50	55.7	57.3	73.2	88.0	100.6	74.9
6 Month N=50	61.0	61.9	74.8	92.2	102.5	78.5
12 Month N=50	59.6	64.2	76.1	91.0	103.8	78.9

6.6.3. Effect of Low Frequency Hearing Loss on Outcomes

As mentioned above primary and secondary outcomes clearly indicated the effectiveness of the Hybrid L24 Implant System. However, when the primary endpoint test measures were stratified by low frequency PTAs at 6 months (see Figure 24), significant differences in outcomes were evident. In order to more adequately review the impact of hearing status postoperatively, a statistical analysis (ANOVA) was conducted on the individual pre and 6 month CNC and AzBio scores (in Acoustic Alone and Hybrid Modes) as a function of the degree of low-frequency hearing loss at the 6 month endpoint. The analysis showed a significant effect for degree of hearing sensitivity. That is, pre- to postoperative level of improvement depended on the degree of hearing maintained at the 6 month postactivation interval. The statistical analyses supported condensing the five categories used throughout the study to quantify hearing into two groups. As illustrated in Figure 25, Group 1 refers to the 33 subjects who presented with severe or better (moderate, moderately-severe, and severe) low frequency hearing and

Group 2 refers to 15[26] subjects who presented with profound or total low frequency hearing loss at the primary endpoint of 6 months.

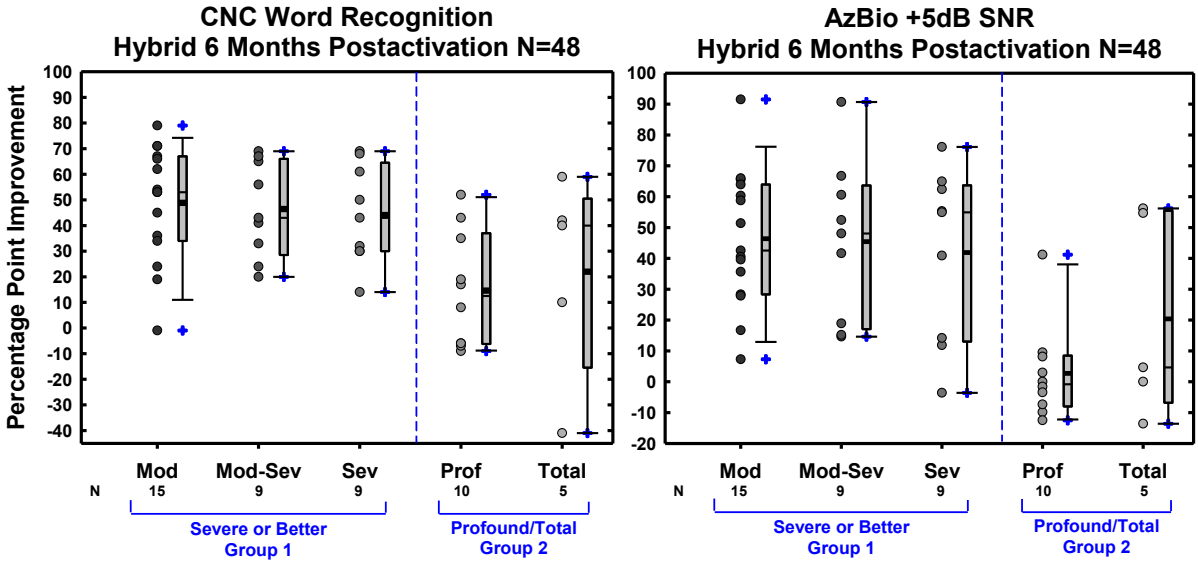

Figure 24: Pre- to 6 month postactivation Hybrid Mode outcomes for the CNC test (upper) and AzBio in noise (lower), as a function of degree of hearing loss at 6 months. Boxes enclose the interquartile ranges, the whiskers bound the 10th and 90th percentiles, with 5th and 95th percentiles indicated by the plus symbols.

Data below will be presented in this section for Groups 1 and 2 for speech perception, music perception abilities and self-assessment outcomes. The graphs presented reflect the performance in the Hybrid Mode and the Combined Mode[27]. The Combined Mode is very important as it reflects the hearing used in everyday life, which in all cases is the use of electric stimulation and all available acoustic stimulation. For Group 1, Combined

[26] The reason the subject population (N=48) in Figures 23 and 24 is different from that above in Table 16 is while only 1 subject did not complete efficacy testing at 6 months, 2 subjects did not complete hearing sensitivity measures thus preventing the inclusion of that '48th' subject into one of the two 'Groups'. For purposes of clarification, imputing their hearing sensitivity thresholds forward to the 6 month endpoint would place the 2 subjects into Group 2 as seen in Table 16.

[27] For the Group 2 subjects, ten of the 15 subjects did not use the Acoustic Component of the L24 system and thus were listening in the 'Bimodal Mode' of electric at one ear and acoustic at the other. This was still their 'everyday listening' condition and for the purposes of the data presentation, Group 2 will still be referred to as 'Combined mode'. When presenting data for the Hybrid Mode, for these same 10 subjects the true listening mode was Electric Stimulation alone.

Mode is the use of the Hybrid (E+A) in the implant ear and acoustic in the contralateral ear. For Group 2, combined, primarily, is the use of electrical stimulation (CI) in the implant ear and acoustic in the contralateral ear (Bimodal Mode). Demographic data is summarized in Table 17.

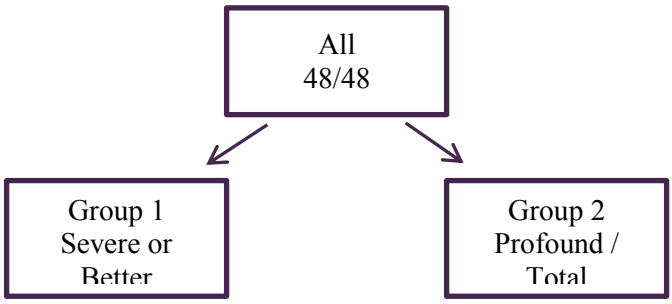

Figure 25: Subgroupings of the study subjects based on hearing sensitivity outcomes at 6 months postactivation.

Table 17: Demographics for Group 1 (Severe or Better) and Group 2 (Profound/Total).

Demographic Characteristics	Group 1 Mean ± SD N (min, max)	Group 2 Mean ± SD N (min, max)
Age at CI in Years	61.8 ± 15.2 15 (37.5 – 86.2)	68.4 ± 14.0 15 (23.0 – 85.7)
Duration of Overall Hearing Loss in Years	25.5 ± 13.1 33 (3.4 – 52.4)	31.8 ± 18.1 15 (13.1 – 74.0)
Duration of High Frequency Hearing Loss in Years	13.0 ± 7.4 33 (1.6 – 30.1*)	11.9 ± 6.3 15 (1.8 – 25.1*)
Male	13/33 (39.0%)	11/15 (73.0%)
Female	20/33 (61.0%)	4/15 (27.0%)
Cause of Hearing Loss:		
Unknown	18/33 (55.0%)	6/15 (40.0%)
Noise Exposure	7/33 (21.0%)	3/15 (20.0%)
Familial	5/33 (15.0%)	4/15 (27.0%)
Autoimmune	1/33 (3.0%)	0/15 (0.0%)
Familial/Otosclerosis	1/33 (3.0%)	0/15 (0.0%)
Fever	1/33 (3.0%)	0/15 (0.0%)
Noise Exposure/Viral	0/33 (0.0%)	1/15 (7.0%)
Ototoxic Drugs	0/33 (0.0%)	1/15 (7.0%)
Preoperative LF PTA (Implanted Ear):		
Normal (0 – 25 dB HL)	1/33 (3.0%)	0/15 (0.0%)
Mild (26 - 40 dB HL)	12/33 (36.0%)	1/15 (7.0%)
Moderate (41 – 55 dB HL)	17/33 (52.0%)	8/15 (53.0%)
Moderate-Severe (56 – 70 dB HL)	3/33 (9.0%)	6/15 (40.0%)

* One subject had < 30 years duration of severe to profound high frequency loss at candidacy assessment but was slightly over 30 years duration by surgery was approved.

6.6.3.1. CNC Word Recognition for Group 1 (Severe or Better) and Group 2 (Profound/Total)

Figure 26 plots preoperative and 6 month postactivation mean scores for Groups 1 and 2 for the CNC Word Recognition Test. Significant pre- to postoperative improvement was evident in both Groups 1 and 2 in both implant ear (left graph) and combined modes (right graph). The Combined Mode performance of Group 2 improved by 28% over the Hybrid Mode. It is important to consider that when making use of the Hybrid cochlear implant in concert with all available acoustic hearing, significant improvement was noted for both those subjects with severe or better levels of low frequency hearing *and* those with profound/total loss of hearing.

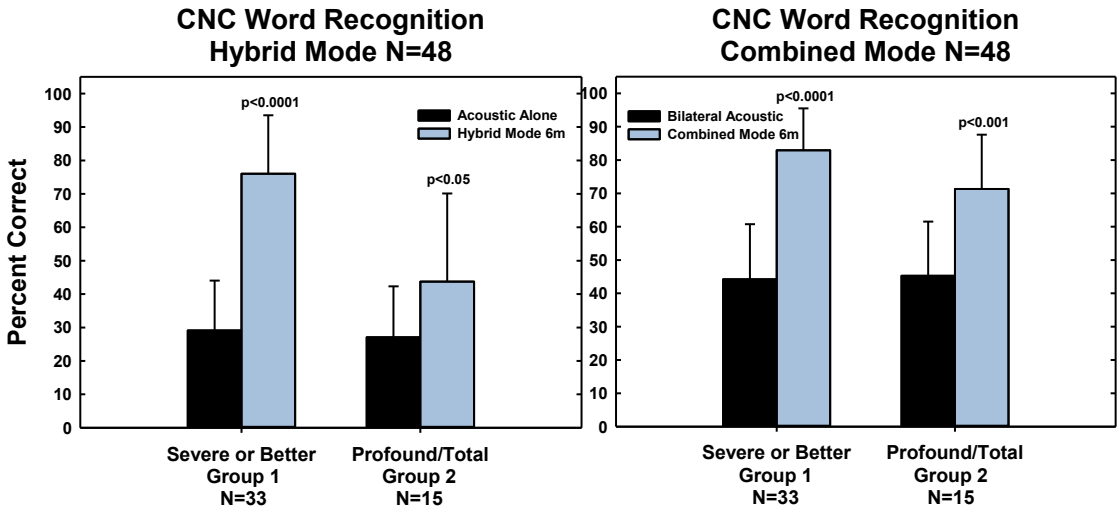

Figure 26: Pre- and 6 month postactivation mean scores for the CNC test for Groups 1 (Severe or Better) and 2 (Profound/Total). The graph to the left shows outcomes for the Hybrid Mode and the graph on the right shows outcomes for the Combined Mode.

6.6.3.2. AzBio Sentence Recognition in Noise for Group 1 (Severe or Better) and Group 2 (Profound/Total)

Figure 27 plots preoperative and 6 month postactivation mean scores for Groups 1 and 2 for the AzBio Sentences in Noise Test. As with the CNC test significant pre- to postoperative improvement was evident in both Groups 1 and 2 in both Hybrid Mode (left graph) and Combined Mode (right graph). Significant improvement was observed in mean performance for both groups with the exception of the Hybrid Mode condition for Group 2. The Combined Mode improved performance for Group 2 by 25 percentage points. It is important to consider that when making use of the Hybrid cochlear implant in concert with all available acoustic hearing, significant improvement was noted for both

those subjects with severe or better levels of low frequency hearing *and* those with profound/total loss of hearing.

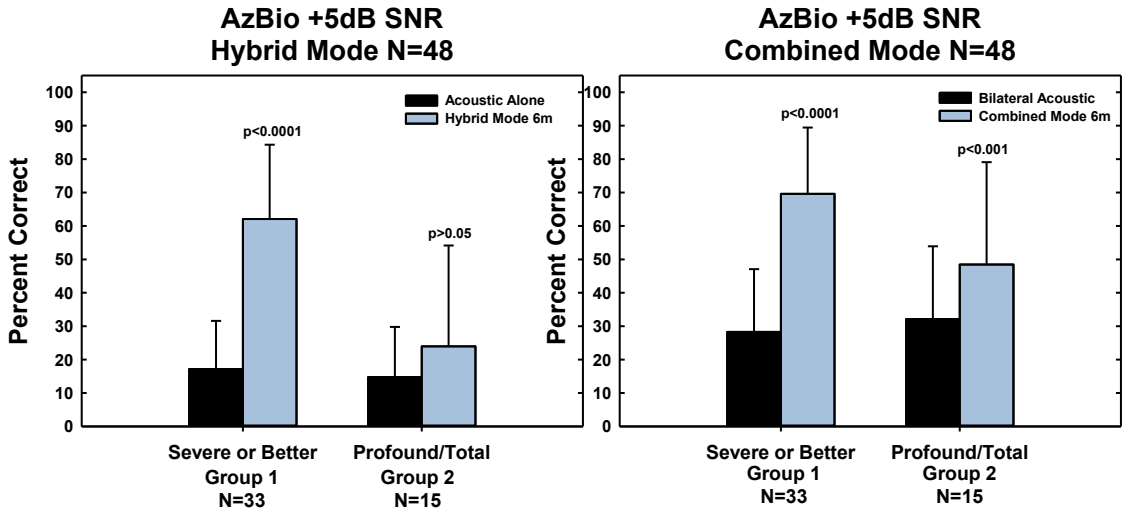

Figure 27: Pre- and 6 month postactivation mean scores for the AzBio sentences in noise test for Groups 1 (Severe or Better) and 2 (Profound/Total). The graph to the left shows outcomes for the Hybrid Mode and the graph on the right shows outcomes for the Combined Mode.

6.6.3.2.1. University of Washington Clinical Assessment of Music Perception (UW-CAMP)

When comparing the preoperative outcomes for each of the three subtests (Implant Ear, only) to the 6 month endpoint, outcomes for the UW-CAMP, results were very similar for Groups 1 and 2. Both Groups retained their music related capabilities pre- to postoperatively across the subtests in both the Hybrid and Combined Modes. While Group 2 trended somewhat poorer than Group 1, there was no significant difference across the subtests except for Pitch (p=0.02) in the Hybrid Mode (Figure 28). In the Combined Mode, the pitch perception scores demonstrated that the addition of the acoustic hearing in the contralateral ear resulted in restoration of pitch perception abilities. In other words, they retained pitch perception scores comparable to that measured preoperatively with bilateral hearing aids. No significant decline was evident for melody or timbre recognition in the unilateral (implanted ear) or bilateral conditions for those in Group 2. Of note, when Group 2 was compared to the results on each subtest to those of conventional cochlear implant users, the outcomes were equivalent or better.

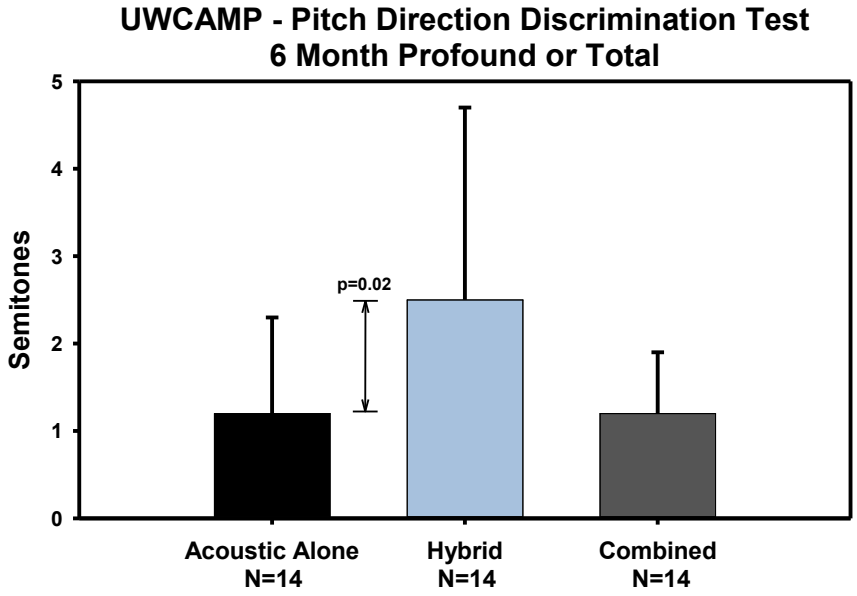

Figure 28: Group 2 (Profound/Total) mean pitch discrimination scores for preoperative versus Implant Ear postoperative to the left, and for the Combined Mode to the far right.

6.6.3.2.2. Speech, Spatial, and Qualities of Sound (SSQ) Questionnaire

The SSQ outcomes for Groups 1 and 2 indicated considerable differences in perceived performance as shown in Figure 29. Group 1 showed significant improvement across all three subscales and the total score. While Group 2 showed no significant improvement on any subscale.

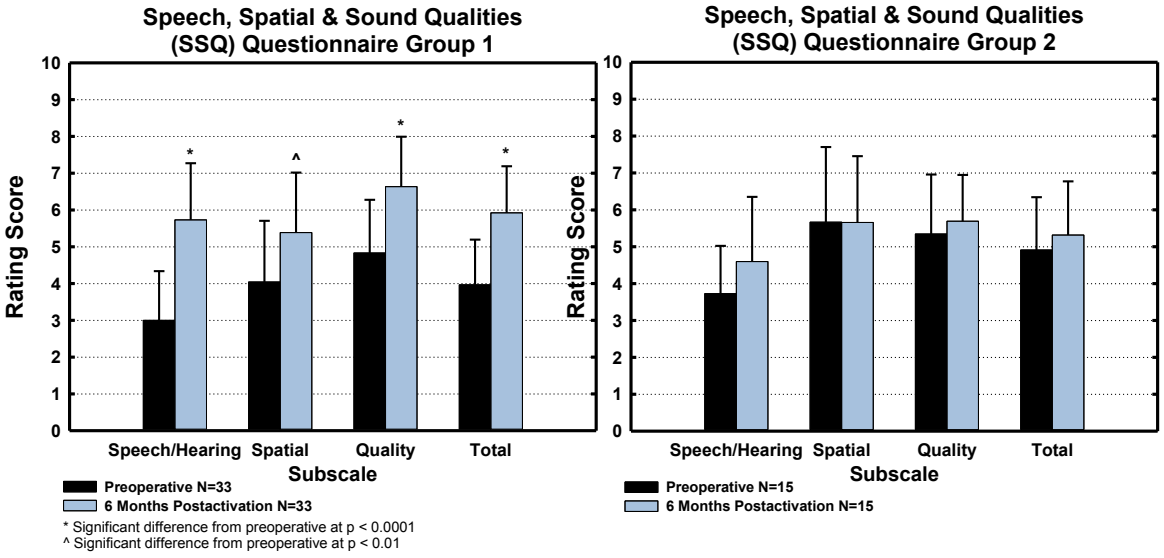

Figure 29: Mean Pre- and Postoperative SSQ Scores for Group 1 (left) and Group 2 (right).

6.6.3.2.3. Device Use Questionnaire (DUQ)

As described in Section 6.4.4.2.2, subjects in the Hybrid L24 clinical investigation reported the use of both ears as their preferred listening mode. Group 1's satisfaction with their hearing performance improved significantly with the Hybrid L24. Only 3% of Group 1 reported being satisfied/very satisfied with hearing aid performance preoperatively. Their satisfaction increased dramatically to 91% being satisfied/very satisfied with the Hybrid L24. Conversely, 53% of Group 2 subjects reported being satisfied/very satisfied with their performance at 6 months. Although lower than that observed for Group 1, this more than doubled the level of satisfaction, 13%, reported preoperatively.

In conclusion, both groups demonstrated improvements in speech perception and device satisfaction at 6 months when compared to the preoperative Bilateral Acoustic condition, particularly when one takes into account that the subjects had access to all available acoustic and electric hearing in *both* ears (Combined Mode). In other words, even in cases of profound or total loss of hearing in the implanted ear, improvement was still observed in most cases when the subjects used the Hybrid L24 Implant with contralateral acoustic hearing (Bimodal Mode), when compared with the preoperative Bilateral Acoustic condition.

- Group 1 subjects demonstrated better performance and satisfaction than the Group 2 subjects who primarily made use of electric hearing in the implanted ear.

- However, for the group who experienced total or profound hearing loss (Group 2), 100% performed equal to or better in the Combined/Bimodal Mode than the preoperative Bilateral Acoustic Mode, as indeed the entire subject group did as shown in Section 6.4.3 (Secondary Endpoint Analyses).

6.6.4. Reimplantations[28]

Four subjects who experienced a profound hearing loss with concomitant decreases in speech perception (compared to preoperative) and dissatisfaction with the Hybrid L24, elected to undergo revision surgeries to have the implant replaced with a traditional cochlear implant. One subject, [redacted], had a suspected device issue related to partial electrode shorting across most of the Hybrid electrode array but explant analyses of the device indicated "no fault found." Table 18 provides a summary of the subjects' implant/revision histories.

Table 18: Summary of reimplanted subjects' history.

Site ID	Subject ID	Hybrid Surgery Date	Adverse Event	Date of Reimplantation	Reason for Reimplantation	Current Status
1523	[redacted]	01/05/2011	Profound/ Total Loss	6/29/2011	To address possible device issue, hearing loss, and poor performance.	Actively using cochlear implant.
1050	[redacted]	02/10/2011	Profound/ Total Loss	03/8/2012	To address hearing loss and poor performance.	Actively using cochlear implant.
1003	[redacted]	02/26/2011	Profound/ Total Loss	02/6/2013	To address hearing loss and poor performance.	Actively using cochlear implant.
1003	[redacted]	05/04/2011	Profound/ Total Loss	07/18/2012	To address hearing loss and poor performance.	Actively using cochlear implant.

[28] [redacted] and [redacted] were explanted/reimplanted.

Three of the four subjects were reimplanted with the Freedom cochlear implant (CI24RE) and one with the Nucleus 5 (CI512)[29]. Both devices use the "Contour Electrode array."

When comparing speech perception outcomes for each of the subjects from preoperative to Hybrid and their most recent post-revision clinical visit (Table 19), it is evident that all have improved to varying degrees in both listening modes (Hybrid and Combined). Additionally, based on self-assessments, each subject indicated they are now satisfied with their cochlear implant.

Table 19: Summary of reimplanted subjects' efficacy.

Subject ID	Acoustic Alone Preoperative		Hybrid Mode Most Recent Prerevision		Reimplantation Most Recent Postrevision Ear Only	
	CNC Words	AzBio Sentences	CNC Words	AzBio Sentences	CNC Words	AzBio Sentences
[redacted]	27%	9.7%	6% *(3 mo)*	1.4%	43% *(6 mo)*	20%
[redacted]	33%	6.1%	42% *(6 mo)*	5%	63% *(6 mo)*	38.9%
[redacted]	14%	7.7%	5% *(12 mo)*	0%	26% *(1 mo)*	10.5%
[redacted]	23%	0%	29% *(12 mo)*	0%	46% *(6 mo)*	9.2%

[29] [redacted] received the CI512 implant.

7. OTHER CLINICAL STUDY INFORMATION

7.1. Other Hybrid Clinical Studies

In addition to the clinical study of the Hybrid L24 used to support this application, Cochlear has conducted or is in process of conducting two other IDE studies pertaining to electric-acoustic stimulation (E+A) with shorter than traditional electrode arrays. As noted above, the implants in both of these studies used electrode arrays that have a shorter length and fewer active intracochlear electrodes than does the Hybrid L24. The unpublished data from these other Hybrid cochlear implant clinical studies are summarized in the following sections.

7.1.1. Hybrid 6 and Hybrid 10

Beginning in 1999, a single-site feasibility study was initiated at the University of Iowa involving three subjects implanted with a 6 mm array incorporating 6 electrode contacts based on the CI24M receiver/stimulator and sometimes referred to as the Hybrid 6. The subjects implanted under this IDE had severe to profound high frequency sensorineural hearing loss, but residual low-frequency acoustic hearing. Based on the results from the first 3 subjects, the IDE was amended and received approval in 2000 to change the electrode length from 6 mm to 10 mm to see if even better results could be achieved. Four more subjects were implanted with this 10 mm array under the feasibility study. Based on data from these 7 subjects, the 10 mm array was chosen as the design moving forward.

In 2002, approval was received to expand the feasibility study into a multicenter study in order to determine if the initial results from the University of Iowa could be more widely duplicated. During this phase, 25 subjects received the 10 mm array, CI24M-based device then called the Hybrid S8 (6 active electrodes plus 2 ground electrodes) rather than Hybrid 10. In 2005, the IDE was amended to expand 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 has been 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 in this multicenter trial included 87 patients implanted with the10 mm electrode design. The mean age of the subjects was 58.9 years with a range of 19 to 82 years.

The study objective of this multicenter study (Phase 2) was to evaluate the safety and efficacy of the Hybrid system in providing E+A stimulation while maintaining residual hearing in individuals who demonstrated significant residual low frequency hearing and severe to profound high frequency sensorineural hearing loss. Most subjects demonstrated significantly improved scores on word recognition in quiet and sentence recognition in quiet and in noise. Mean scores for all of the speech tests administered at the 6-month-postactivation primary end point were significantly better for than those observed preoperatively, with the strongest effect shown for the everyday listening "Combined Mode," in which subjects used Hybrid input to the implant ear (E+A) combined with a hearing aid in the other ear. A few subjects who did not retain residual hearing used the Bimodal Mode for everyday listening (CI in one ear, hearing aid in the other). Best performances were noted for the 12 month evaluation suggesting that subjects continued to improve beyond the 6 month primary endpoint. APHAB (Abbreviated Profile of Hearing Aid Benefit) results also showed significant perceived improvements for all subscales, and the SQS (Sound Quality Survey) responses clearly indicated that the Combined Mode was preferred in most listening conditions by most subjects and resulted in the best perceived sound quality and speech understanding. A majority of subjects were satisfied with their decision to receive the Hybrid cochlear implant.

7.1.2. Hybrid S12

Based on outcomes with the Hybrid 6 and S8 it was decided to modify the design of the electrode array to include more electrode contacts/channels. This next generation of a Hybrid electrode developed by Cochlear was also 10 mm long, but had four more active electrodes (10 total) on the intracochlear array (with two extracochlear) and the addition of a non-stimulating platinum collar. These changes were made to provide increased spectral density of electrodes across the basal region of the cochlear. This electrode array, called the Hybrid S12 (10 active electrodes plus 2 ground electrodes), is currently undergoing investigational study under an IDE.

In this single-subject repeated measures study, candidates were assessed in the unaided and aided (i.e., with hearing aids) conditions preoperatively. Postoperatively, acoustic alone and E+A modes are tested to evaluate the usefulness of electric combined with acoustic stimulation for those individuals who maintained low frequency hearing. Speech recognition tests (Speech Reception Thresholds or SRT, CNC words, and AzBio sentences in noise) are being used to assess hearing performance over time and pure tone audiometric thresholds are obtained to evaluate the impact of implantation on residual low frequency hearing thresholds. In addition, the UW-CAMP music test along with subjective questionnaires [(Speech, Spatial, and Sound Quality questionnaire (SSQ) and a

custom Device Use Questionnaire (DUQ)] are administered at the 6- and 12-month intervals.

Mean scores for all of the speech tests administered at the 6-month postactivation primary endpoint were significantly better than those observed preoperatively. SRTs for both the ipsilateral and contralateral noise conditions demonstrated significant improvement from the preoperative measurements. The UW-CAMP (pitch, melody, and timbre subtests) was not statistically significant between preoperative and postoperative, but the SSQ responses indicated that the Combined Mode was preferred in most listening conditions for most subjects and resulted in the best perceived sound quality and speech understanding.

As of December 31, 2012, there were no unanticipated adverse events in the study.

7.2. Relevant Unpublished Data on the Hybrid L24

The Hybrid L24 electrode array is longer than the first three Hybrid electrode arrays, at 15 mm active length, and has a full complement of 22 active electrodes (plus 2 extracochlear), like Cochlear's longer arrays. The IDE clinical study results for the Hybrid L24 study are described in Section 7 of this submission, but there have also been two studies of the Hybrid L24 Implant System completed outside of the United States. The first was a multicenter European study in support of obtaining the CE mark and the second study was in Australia.

7.2.1. European Clinical Trial

In 2006 Cochlear initiated a multicenter study (16 centers) in the European Union to support its application for the CE mark of the Cochlear Hybrid L24. Subjects were 66 adults (aged 21 to 81) implanted with the Hybrid L24 Implant and receiving electric-acoustic stimulation (E+A). The objectives of the study were: 1) to measure the preservation of residual hearing in subjects who received the Hybrid L24 implanted through the round window and 2) to investigate the postoperative performance of the Hybrid subjects in their "best-aided condition[30]" as compared to their best-aided preoperative performance.

[30] Could have been the Hybrid Mode, Combined Mode or the Bimodal Mode.

Endpoints were defined as the average differences in low-frequency (125 Hz – 500 Hz) thresholds measured between preoperative and 12 months postoperative, and the average gain in speech recognition scores as measured in quiet and in noise in the best-aided condition at 1 year postoperatively compared to the preoperative condition. This study also included secondary endpoints to address any differences between the "best-aided" condition and the "implant-alone" or Hybrid Mode conditions. Additionally, testing was conducted on a subset of 19 subjects to determine possible benefits for spatially separated speech and noise, and for music.

Initial subjects were fit with a Freedom Sound Processor at the implant ear, postoperatively, and a commercial In-The-Ear (ITE) hearing aid. Beginning in 2008 the EASPID (Electric-Acoustic Speech Processor Investigational Device) became available. It included a Hybrid Freedom Sound Processor coupled to a RITE (Receiver-In-The-Ear) component that delivered the acoustic stimuli ipsilaterally.

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 patients enrolled and implanted, 61 completed the 12-month post-operative study duration. The mean age at enrollment was 53 years with a mean duration of severe-to-profound high frequency hearing loss of 13.4 years. Seventy-nine percent of subjects were female. Seventy-seven percent of subjects wore bilateral hearing aids prior to implantation.

The percent correct word recognition score was measured in quiet at a 70 dB SPL presentation level. For noise testing, the noise level was fixed at both 70 dB SPL and 60 dB SPL noise levels, with a 10 dB signal-to-noise ratio (SNR). Note that some centers chose to use an adaptive SNR test approach instead. Percent correct speech scores were compared in two ways; first, group mean differences for different visits/conditions were subjected to ANOVA with additional post-hoc comparisons (non-parametric); second, proportion of scores with a difference between conditions/intervals of at least 20% were calculated. Twenty percentage points was considered clinically and statistically significant when considering an individual's scores for different conditions and intervals. Speech materials were presented in the native language(s) of the subjects.

Performance was evaluated in in the best aided condition preoperatively using both ears, and postoperatively using the implant plus either one or two ears acoustically. Final test conditions (best-aided) could therefore be the Hybrid (implant and acoustic ipsilaterally), Combined (implant and bilateral acoustic) or Bimodal (implant with acoustic at contralateral ear only).

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, 73% showed thresholds decreased ≤ 30 dB at 500 Hz and 43% were ≤ 10 dB at 500 Hz (N = 61). The report indicates that thresholds at 125 and 250 Hz were highly correlated with those at 500 Hz.

Due to site-specific equipment variability, not only was speech-in-noise testing language specific but also test condition specific. The researchers applied multiple statistical methodologies to account for the differences. Results indicated that 73% of subjects improved by at least 20% on their speech recognition scores in noise at 12 months postoperative compared to preoperative. At the 12-month interval, 88% of the tested subjects used Hybrid stimulation. Analysis of variance showed that all mean differences between pre-operative and post-operative intervals were statistically significant. 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, there were also significant benefits of the Hybrid implant shown with questionnaire data (SSQ and Health Utility Index or HUI).

Limited spatial separation studies conducted at just two centers indicated, overall, that subjects experienced a release from masking when the acoustic information was presented to the implant ear (Hybrid condition). A music perception test (MACarena), also used at only one site with limited subject numbers, indicated that subjects received additional benefit in the Hybrid mode vs. the Bimodal mode on the two subtests evaluated.

In this study, two of the 66 subjects were implanted via cochleostomy and 64 via round window insertion. Insertion of the electrode was rated by the surgeons “easy” or “very easy” in 69% cases, and “acceptable” in 24%.

Twelve adverse events were reported over the course of the study. Seven were serious events, and four were or possibly were related to the device or surgery. All seven were resolved. Three non-device-related serious adverse events required subsequent hospitalization, with one subject dying from unrelated causes due to a tumor. There was one report of a “nervous” condition that ultimately resulted in subject withdrawal.

The authors concluded that the Hybrid implant with EASPID had been proven beneficial for subjects with residual hearing in their implant ear.

7.2.2. Australian Clinical Trial

Beginning in 2005, a clinical study was initiated at The Hearing Cooperative Research Center (CRC) in Melbourne, Australia with the Hybrid L24 Implant System. 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 Implant System. This was to be measured, preoperatively and postoperatively, with audiometric thresholds (measured 125 Hz -1000Hz, only) and speech perception testing (in quiet and noise) over a period of 12 months. The acoustic device to be used in the implant ear was either the subject's own hearing aid, the ITE device (Phonak) or a Freedom for Hybrid Sound Processor (Cochlear).

This single-subject, repeated measures design study enrolled and implanted 13 subjects with one withdrawal (due to advancing Alzheimer's symptoms) unrelated to the device or procedure. Subjects were evaluated with open-set speech test materials [CNC words and CUNY sentences (in noise)] preoperatively and at each of the postoperative test intervals (activation, 3 months, 6 months and 12 months). The source for the 'noise' was a competing babble test composed of four-talker babble, offset and superimposed to present as eight-talker babble. The speech material was presented in the sound field at 60 dB SPL and 65 dB SPL for the word and sentence materials, respectively. The test conditions for speech included monaural and binaural with hearing aids preoperatively and then a Combined Mode (Hybrid L24 + acoustic at implant ear and acoustic only at non-implant ear); Hybrid Mode (Hybrid L24 + acoustic at implant ear) and finally the monaural acoustic mode (acoustic only on the implant ear) at all postoperative intervals. The mean age of the subjects was 67.5 years with a range of 47 to 82 years.

Results at activation revealed that 9 of the 13 subjects had a mean change from preoperative of ≤ 15 dB. Over the next twelve 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[31] saw a shift in hearing of ≤ 30 dB HL while 8 of 12 experienced only a shift of ≤ 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

[31] One subject withdrew at 3-month interval due to Alzheimer's disease

preoperative (acoustic [hearing aid] in implant ear) score of 8% was in contrast to the Hybrid (L24 + acoustic at implant ear only) group mean score postoperatively of 35.8%; in the Combined Mode (L24+ acoustic at implant ear and acoustic at non-implant ear), the preoperative of 16.4% (bilateral acoustic aids) 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 at 12 months of 70.4%.

Six subjects experienced adverse events with one withdrawing (Alzheimer subject); one experiencing illness requiring hospitalization with labyrinthitis accompanied by hearing loss and the remaining 4 four subjects experiencing temporary events consistent with cochlear implant labeling and all resolving by the end of the study.

The study conclusion was that the Hybrid L24 presented potential for use in preserving hearing and improved speech outcomes for the majority of subjects, postoperatively.

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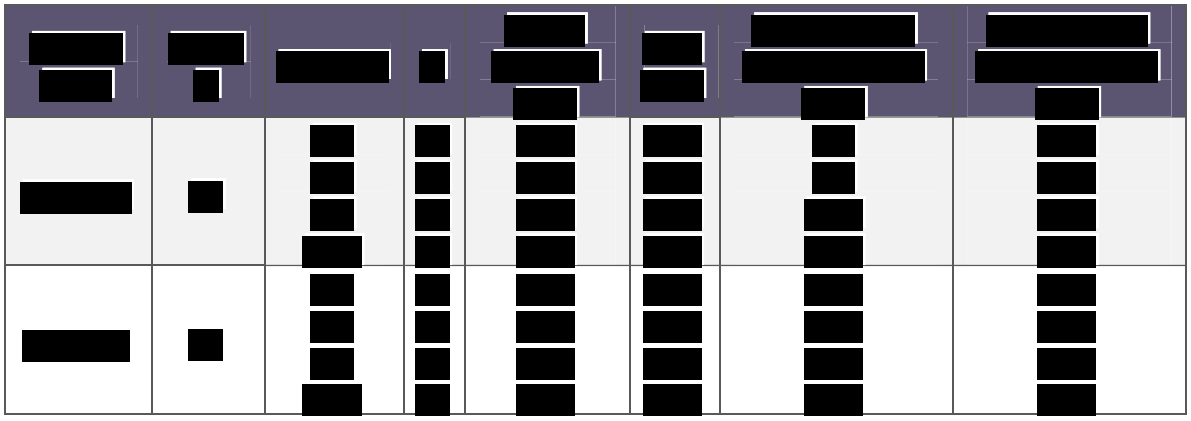

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8. BENEFIT – RISK ASSESSMENT OF THE HYBRID L24 IMPLANT SYSTEM

The criteria set forth in 21 CFR 860.7 to establish safety and effectiveness of a device includes the assessment of the probable benefit from use of the device in compliance with its indications against any probable injury or illness from that use. The mechanism for this determination, or benefit-to-risk assessment, is based upon '…valid scientific evidence…' through well-controlled clinical investigations and confirmation that the device is manufactured in accordance with 21 CFR Part 820 (including nonclinical tests such as biocompatibility, electrical, EMC, and mechanical). The Hybrid L24 Implant System meets these criteria, and the benefit-risk assessment supports approval of the product.

8.1. Assessment of the Benefit

The intended use population for the Nucleus Hybrid L24 Implant System is those with ski-slope hearing loss as defined earlier in this document. As described in Section 2, treatment options include broadband and frequency lowering (i.e., hearing technology that transposes or compresses inaudible high frequency information into lower frequency regions of more functional acoustic hearing) hearing aids or the option of no hearing aid(s). The subjects in the Hybrid L24 clinical investigation were all users of a broadband or frequency lowering (FL) hearing aid. As demonstrated in the preoperative test condition, hearing aids do provide a level of benefit but 76% (38/50) of the subjects in the trial expressed dissatisfaction with their performance with hearing aids prior to implantation.

The Hybrid L24 clinical study demonstrated several benefits of the Hybrid L24 Implant System as compared to hearing aids for this type and degree of hearing loss, including improvements in word and phoneme understanding in quiet and sentence understanding in noise. These improvements are likely to be experienced by most individuals who meet the device's indications for use.

The study met its two primary and secondary efficacy endpoints. That is, the mean improvements observed pre- to postoperatively, were significant for both primary endpoint measures, CNC monosyllabic word recognition and AzBio sentence recognition in noise, for the implanted ear.

At 6 months postactivation, the subjects experienced:

- In the Hybrid Mode[32] :
  - A statistically significant improvement ($p < 0.0001$) in word recognition in quiet at the 6 month endpoint was observed, with mean CNC monosyllabic word scores improving from 28.4% in the preoperative Acoustic Alone Mode to 65.4% in Hybrid Mode.
  - A statistically significant improvement ($p < 0.0001$) in sentence recognition in a difficult noise environment (+5 dB SNR) at the 6 month endpoint was observed, with mean AzBio Sentence scores improving from 16.3% in the preoperative Acoustic Alone Mode to 49.2% in Hybrid Mode.

In addition, secondary endpoints were met in that more than 75% of the subjects implanted with the Hybrid L24 Implant System performed equal to or better than they did in the preoperative Acoustic Alone condition.

Specifically:

- 98% (48/49) of subjects performed equal to or better postoperatively for CNC word recognition.
- 91.8% (45/49) of subjects performed equal to or better postoperatively for CNC phoneme recognition.
- 89.8% (44/49) of subjects performed equal to or better postoperatively for sentence recognition in noise at a +5 dB SNR as measured with AzBio sentences.

Although the primary endpoints of the study were related to the Hybrid Mode (i.e., the implanted ear alone) for testing purposes, the Combined Mode, where both ears are used with all available stimulation, is the listening condition normally used by individuals on an everyday basis.

[32] Hybrid Mode refers to the implant ear only being tested preoperatively, with an appropriately fit hearing aid, and postoperatively with the Hybrid L24 Implant and Acoustic Component. The data presented includes all subjects whether or not the sound processor incorporated acoustic amplification at the implanted ear.

At 6 months postactivation, the subjects experienced:

- In the Combined Mode[33]:
  - A statistically significant improvement ($p < 0.0001$) in word recognition in quiet at the 6 month endpoint, with mean CNC Word scores improving from 44.9% in Bilateral Acoustic Mode preoperatively to 79.4% in Combined Mode.
  - A statistically significant improvement ($p < 0.0001$) in sentence recognition in a difficult noise environment (+5dB SNR) at the 6 month endpoint, with mean AzBio Sentence scores improving from 29.6% in Bilateral Acoustic Mode preoperatively to 62.6% in Combined Mode.
- Substantial improvements in aided thresholds in the high frequency range in the Hybrid Mode compared to the preoperative Acoustic Alone Mode.
- Positive self-reported outcomes and increased satisfaction, in the majority of cases, based on questionnaire data.

In this study, no subject showed a significant decrement pre- to postoperatively in the condition that they use every day. In other words, 100% of the subjects performed equal to or better than they did preoperatively in the Bilateral Acoustic Mode when compared to the Combined Mode at the 6 month endpoint.

Even considering the group of subjects who experienced a profound or total loss of low frequency hearing, resulting in their inability to use amplification in the implanted ear, significant improvements in mean speech perception outcomes were observed compared to preoperative amplification (hearing aids) in both the Acoustic Alone and Bilateral Acoustic conditions.

Finally, Hybrid implantation also provided an opportunity to maintain music perception abilities, which would be compromised by cochlear implantation. On an assessment of music perception, Hybrid subjects maintained their music perception abilities on measures of pitch discrimination, familiar melody recognition, and timbre recognition.

[33] Combined Mode refers to both ears being tested preoperatively, with appropriately fit hearing aids, and postoperatively with the Hybrid L24 Implant and acoustic stimulation in both ears. The data presented includes all subjects whether or not the sound processor incorporated acoustic amplification at the implanted ear (Bimodal Mode).

Typical cochlear implant users are not able to attain the same level of music perception following implantation[34].

8.2. Assessment of the Risks

The surgical procedure for the Hybrid L24 Implant is essentially the same as for the widely marketed Nucleus 24 (CI24RE) cochlear implant (P970051) including the approach to the cochlea, whether by a cochleostomy, as in the referenced clinical trial, or by a round-window approach as used in a European Hybrid clinical trial. It is therefore not unexpected that the severity, type and number of adverse events related to the device and/or procedures are few and consistent with those from the clinical study that assessed the Freedom cochlear implant. Additionally, none of the adverse events were determined to be serious in nature, and there were no unanticipated adverse device effects reported.

The only difference in adverse events reported between the Freedom study and the Hybrid L24 study were reports of significant loss of residual hearing at the implant ear. As cochlear implants are expected to eliminate all residual hearing in the implanted ear, assessment of hearing after implantation with the Freedom cochlear implant was not a metric gathered during that study (See Section 6).

Assessment of acoustic hearing following implantation with the Hybrid L24 Implant was completed as part of this study. A summary of low frequency hearing sensitivity using a 5 frequency average of 125 through 1000 Hz at the 6 month test interval is below:

- 33 subjects maintained hearing of a severe degree or better:
    - 15 experienced a moderate (41 through 55 dB HL) low frequency hearing loss by 6 months postactivation
    - 9 experienced a moderate to severe (56 through 70 dB HL) low frequency hearing loss by 6 months postactivation
    - 9 experienced a severe (71 through 90 dB HL) low frequency hearing loss by 6 months postactivation
- 17 experienced a decrease in low frequency hearing resulting in profound or total loss of hearing:

[34] Kang, S.Y., Nimmons, G.L., Drennan, W., Longnion, J., Ruffin, C., Nie, K., Won, J.H., Worman, T., Yueh, B., Rubinstein, J. (2009). Development and validation of the University of Washington clinical assessment of music perception test. *Ear Hear*, 30(4), 411-418.

- 12 experienced a profound (> 90 dB HL) low frequency hearing loss by 6 months postactivation
- 5 experienced a total (nonmeasurable) low frequency hearing loss by 6 months postactivation

As noted above, even for subjects unable to use low frequency amplification due to a significant (or total) loss of low frequency hearing, improvements in speech perception outcomes compared to preoperative amplification (hearing aids) were observed in both the unilateral and bilateral conditions. As stated above no subject showed a significant decrement in speech perception pre- to postoperatively in the condition that they use every day. In other words, 100% of the subjects performed equal to or better than they did preoperatively in the Bilateral Acoustic condition when compared to the Combined Mode at the 6 month endpoint. In addition, low frequency acoustic hearing sensitivity was preserved at a level sufficient for amplification use in the implant ear in 74% of subjects at the 6 month endpoint.

Four subjects[35] elected explantation of their Hybrid L24 Implant and pursued reimplantation with a cochlear implant having a longer electrode array. The risks of a second surgical procedure were no different than those present in current cochlear implant practice.

8.3. Risk Mitigation

As with other cochlear implants, providing clear and unambiguous surgical instructions within the labeling is important for the surgeon. While the characterization and severity of the adverse events within this study are consistent with those in the Freedom cochlear implant, the exception were those significant losses of low frequency residual hearing that accounted for 22 of the reported events. In an attempt to determine whether or not baseline characteristics were an associated risk for any of the adverse events, appropriate analyses were conducted and results yielded no evidence of a predisposition for adverse events, including postoperative profound or total loss of hearing. Since the first approvals for individuals with severe hearing loss, labeling and potential candidate counseling for all cochlear implants included appropriate 'Warnings and Precautions' stating that all residual hearing would be lost. However, for this intended population it is very important for individuals to be advised of the risks and benefits associated with the

[35] All experienced a profound/total loss of residual hearing at some point postimplantation.

treatment when loss of residual hearing occurs and when it is maintained. The company has included data describing the rate and severity of postoperative hearing loss observed in the clinical trial in the proposed Hybrid L24 labeling. The labeling conveys both the magnitude of the changes observed, as well as the classification of the resulting low frequency hearing.

8.4. Summary and Conclusions

The Hybrid L24 Implant represents a new treatment option, the first truly integrated electric-acoustic solution, for a patient population that has traditionally only been offered acoustic hearing treatment options. The device offers improvements in speech understanding that outweigh the risks associated with surgery, and the potential degradation of acoustic hearing in the implanted ear. The study met its primary and co-primary efficacy endpoints as described throughout this document.

While the impact of the proposed treatment on subjects' existing hearing in the implanted ear is an important consideration, the primary goal of surgical intervention with the Hybrid L24 Implant System is to improve the speech recognition abilities in the individuals with ski-slope hearing loss receiving the device. That being the case, the retention of low frequency hearing is necessarily a secondary objective; if low frequency hearing is maintained, but speech recognition is not improved, the treatment is not achieving its stated goals. In contrast, if speech recognition improves despite the loss of hearing, the treatment can still be considered successful, as the individual's communication abilities are still enhanced by the device. Certainly the most desirable outcome is that speech recognition is enhanced while low frequency hearing is maintained, but Cochlear believes that making retention of low frequency hearing the primary consideration in the risk/benefit analysis misconstrues the intent of the treatment, and is inconsistent with the individual's goals when they seek out this treatment.

The indications for cochlear implantation have shown a steady increase in the degree of hearing and speech perception abilities since the introduction of the first multichannel cochlear implants in the mid-to-late 1980s. With each change in indication, individuals with greater levels of acoustic hearing, preoperatively, have been implanted and have demonstrated improved communication, well beyond environmental-sound awareness. Electric-acoustic devices represent a novel approach to this issue by providing the benefits of electrical stimulation for individuals with profound high frequency ski-slope hearing loss, while providing a reasonable probability that existing low frequency hearing will be kept.

The Hybrid L24 Implant provides a more successful treatment option for suitable candidates than hearing aids. Subjects in the trial were able to combine the high

frequency information provided by the Hybrid L24 Implant, not available to them via hearing aids, with low frequency acoustic information from one or both ears. More importantly as a result of providing important high frequency speech information the subjects demonstrated excellent speech perception outcomes in quiet and in noise, setting a new standard for cochlear implantation. Subjective outcomes were positive, and when considering the patient's everyday listening condition, even measures sensitive to losses in low frequency hearing (such as music perception) were largely unchanged.

Although a percentage of individuals will lose their preoperative low frequency acoustic hearing sensitivity, this is disclosed in the labeling and candidates will be informed of this risk prior to the Hybrid L24 Implant surgery. Further, most individuals who lose residual low frequency hearing can still be expected to receive substantial functional and speech recognition benefit on a daily basis compared to their previous performance with hearing aids, due to the combined benefits that electric-acoustic hearing delivers; regardless of 'where' the respective stimulation comes from. Ideally, acoustic hearing is available to these individuals bilaterally as this delivers the best outcomes. However, even when acoustic hearing is available contralaterally it can be effectively used in concert with electric stimulation to deliver improved hearing outcomes relative to bilateral amplification.

The complex but highly relevant scatter plots shown as Figure 30 and Figure 31 summarize individual endpoint outcomes for the 48 subjects with audiometric and efficacy data for the primary measures at the 6-month endpoint. Figure 30 shows the improvement observed for the AzBio sentence test in noise (Y-axis) as a function of the improvement observed for the CNC word test (X-axis) for each of the 48 subjects. Group 1 and Group 2 subjects are colored as blue and red points, respectively. Circles enclose those subjects who did not use the acoustic component of the Hybrid processor and therefore used electric stimulation alone in the implanted ear at the 6-month endpoint. The horizontal lines enclose the range of change scores for the AzBio test that are nonsignificant based on the binomial model. Scores above the upper horizontal line would therefore indicate individuals who showed significant pre- to postoperative improvement for the AzBio test. The vertical lines enclose the range of scores for the CNC word test that are nonsignificant based on the same model. Scores to the right of right-most vertical line would therefore indicate individuals who showed significant pre- to postoperative improvement for the AzBio test. Optimal outcomes are indicated by the points in the upper right quadrant, meaning improvement was observed on both primary measures. Conversely, poor outcomes are indicated by points in the lower left quadrant, meaning that a significant decrement was observed on both primary measures.

Figure 30 shows that 34 (71%) of the 48 subjects presented with significant improvement for both the CNC and AzBio tests. Only 1 subject, from Group 2 with a profound/total

loss of hearing in the implanted ear, experienced a significant decrement on both measures. As a group, 43 (90%) of the 48 subjects presented with changes in their scores corresponding to postoperative performance that was equal to or better than observed preoperatively Acoustic Alone. Also evident is that the best outcomes were observed for the subjects falling within Group 1, having severe or better levels of hearing, postoperatively.

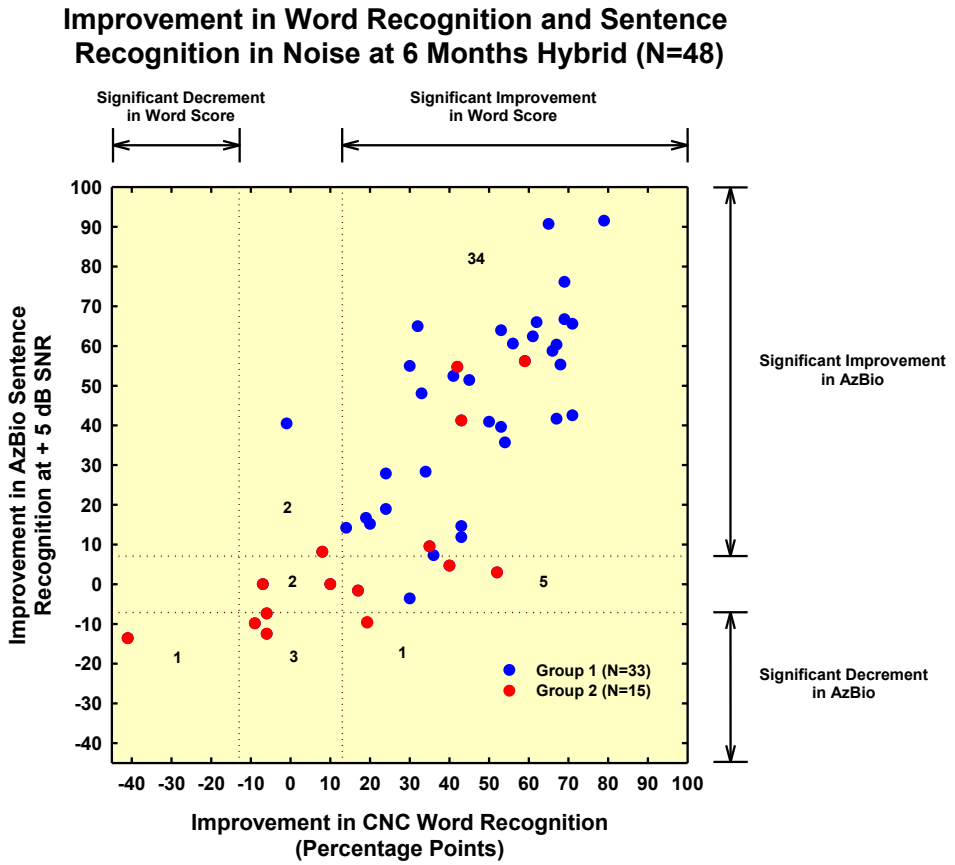

Figure 30: Improvement for the AzBio sentences at +5 dB SNR as a function of improvement for the CNC word test in the Hybrid Mode for Group 1 and Group 2 subjects.

Figure 31 plots data in the same fashion as Figure 30, for the same 48 subjects, except in the Combined Mode. These data are important to appreciate, as they truly represent the optimal listening condition used by the subjects on a daily basis (both ears). Circles enclose those subjects who did not use the acoustic component of the Hybrid processor and therefore used electric stimulation alone in the implanted ear with contralateral acoustic hearing (i.e., the Bimodal Mode). The graph shows that 38 (79%) of the 48 subjects presented with significant improvement for both the CNC and AzBio tests. All 48 subjects (100%) presented with change scores corresponding to postoperative

performance that was equal to or better than that observed preoperatively in the Bilateral Acoustic condition.

Comparing Figure 31 with Figure 30, it is visually evident that the data points shift toward the upper right quadrant. That is, even for subjects not showing improved scores for the treated ear alone, significant improvement is possible when the Hybrid device is used in concert with contralateral acoustic hearing. While still evident that the best outcomes were observed for the Group 1 subjects, most Group 2 subjects also showed significant improvement pre- to postoperative. These data suggest that most subjects who obtain high-frequency information via electric stimulation are able to effectively combine electric and low-frequency acoustic hearing to derive improved speech perception, whether it comes from acoustic hearing in both ears or from the contralateral ear alone.

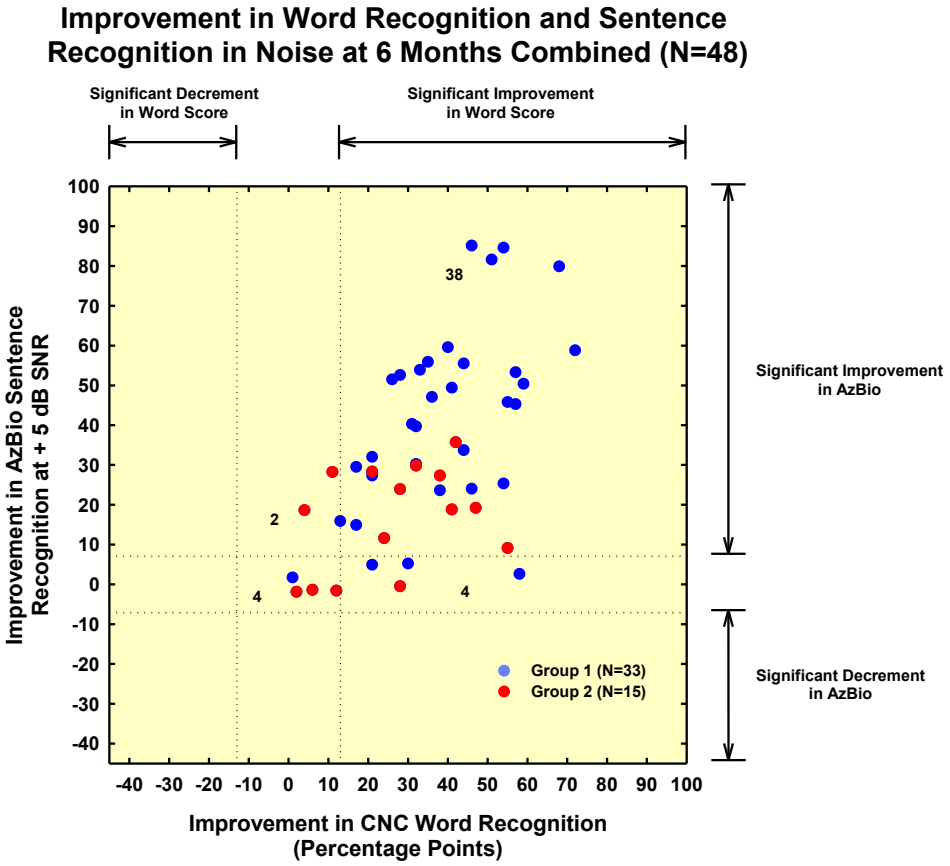

Figure 31: Improvement for the AzBio sentences at +5 dB SNR as a function of improvement for the CNC word test in the Combined Mode for Group 1 and Group 2 subjects.

The results of the clinical investigation support the conclusion that the benefits of the Hybrid L24 Implant System substantially outweigh any risks for those with ski-slope hearing loss falling within the indications for use guidelines proposed.

9. CONCLUSIONS

The Hybrid L24 Implant System represents a new treatment option, the first truly integrated electric-acoustic (EAS) solution, for a patient population that has few current therapeutic alternatives for ski-slope hearing loss. High frequency sound, crucial for speech discrimination, is provided electrically by the Hybrid L24 Implant while residual low frequency hearing is amplified by the acoustic component. The two modes of stimulation are processed and provided simultaneously by the externally worn Nucleus 6 Sound Processor.

Subjects with ski-slope hearing loss that participated in the Hybrid L24 clinical study were able to combine both low (acoustic) and high frequency (electric) information, from one or both ears, provided by the Hybrid L24 Implant System. Results indicated significant speech perception improvements in quiet and in noise when compared to preoperative performance. In fact, the study met all efficacy endpoints, with adverse events occurring at a comparable rate to that of a typical cochlear implant population. At study endpoint (6 months post activation), 100% of subjects showed equal or greater speech perception performance when listening in the Combined Mode. When listening in the Hybrid Mode, 90% of subjects showed equal or greater speech perception performance.

As documented in the clinic study results, a percentage of individuals will lose their preoperative low frequency acoustic hearing as a result of Hybrid L24 implant surgery. This known risk is disclosed in the Hybrid L24 implant system labeling and is strongly recommended as an integral component of preoperative surgical and device counseling. Irrespective of the postoperative hearing status, most individuals can still be expected to receive substantial functional and speech recognition benefit on a daily basis when compared to their preoperative listening configuration of two hearing aids.

In summary, Cochlear believes that the clinical study results demonstrate a reasonable assurance that the Hybrid L24 Implant System is safe (as defined in 21 C.F.R. §860.7(d)(1)), as the probable benefits to health from use of the Hybrid device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. In addition, the study results demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use. Cochlear also believes that the clinical study provides a reasonable assurance that the Hybrid L24 Implant is effective (as defined in 21 C.F.R. §860.7(e)(1)) because, in a significant portion of the target study population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, provides clinically significant results.

The data in this application support the reasonable assurance of safety and effectiveness of this device for individuals 18 years of age and older presenting with normal to moderate hearing loss in the low frequencies with a severe to profound sensorineural loss in the high frequencies and meeting the indications. Based on the clinical study results, it is reasonable to conclude that the clinical benefits with use of the Nucleus Hybrid L24 Implant System in terms of improvement in speech understanding in quiet and noise, and the likelihood of increased satisfaction with sound quality and spatial hearing outweigh the risks associated with the device and surgical procedure through one-year of follow-up when used in the indicated population in accordance with the directions for use.

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11. APPENDICES

11.1. Speech Spatial Qualities Questionnaire (SSQ)

11.2. Preoperative Device Use Questionnaire (DUQ)

11.3. Postoperative Device Use Questionnaire (DUQ)

11.4. Summary of Safety and Effectiveness Data (SSED)

11.5. Nucleus® Hybrid Physician's Package Insert

11.6. Nucleus® Hybrid Surgeon's Guide

11.7. Nucleus® Hybrid Important Information: Warnings, Precautions, and Electromagnetic Compatibility

11.8. Draft Post Approval Study – Extended Duration

11.9. Draft Post Approval Study – Newly Implanted