Volumes 22-25: Clinical Investigations

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1 Introduction

A cochlear implant is a surgically implanted electronic device that uses an electrode array to bypass the damaged hearing sensory cells and electrically stimulate the spiral ganglion cells of the cochlea that innervate the auditory nerve.

A cochlear implant system has two parts: an external sound processor and an internal implant. The internal implant is placed under the skin and behind the ear during a surgical procedure. Part of the internal implant is an electrode array implanted in the cochlea of the recipient. The external sound processor is worn behind the ear. It has an attached cable that terminates in a coil and magnet. When held close to the internal implant, the magnet is attracted to a magnet in the internal implant. The proximity of the two magnets allows the external coil to transmit digital information transcutaneously using an RF signal. The digital information represents sounds in the environment of the cochlear implant recipient. Both the internal implant and external sound processor need to be present for the system to work. If a cochlear implant recipient removes the external sound processor the RF signal is no longer being sent across the skin and he or she will no longer perceive sound using the cochlear implant.

When there is sound in the environment of the cochlear implant recipient, the external sound processor captures it, filters and processes it, and then converts it into digital information that is transmitted to the internal implant. The implant then converts the digital information into an electrical signal and sends the signal to the electrode array in the cochlea. The electrical signal from the implant then stimulates the hearing nerve, bypassing damaged hair cells. See Figure 1 for a description of how the system works.

In some cochlear implant systems known as “Hybrid” configurations, there is also an acoustic component that is capable of providing amplification of sound in the low-frequency region when the patient has retained acoustic hearing sensitivity. It has been widely reported in the literature over the last few years that some cochlear implant patients retain some degree of low-frequency acoustic hearing due to the use of new electrode arrays and insertion techniques that are less traumatic to cochlear structures. This may be even more likely with the Hybrid L24 electrode array rather than a

traditional longer cochlear implant electrode array because a shorter array will cause less damage to the innermost portion of the cochlea; i.e., the electrode array will not reach the apical region of the cochlea that mediates long wavelength, low-frequency signals.

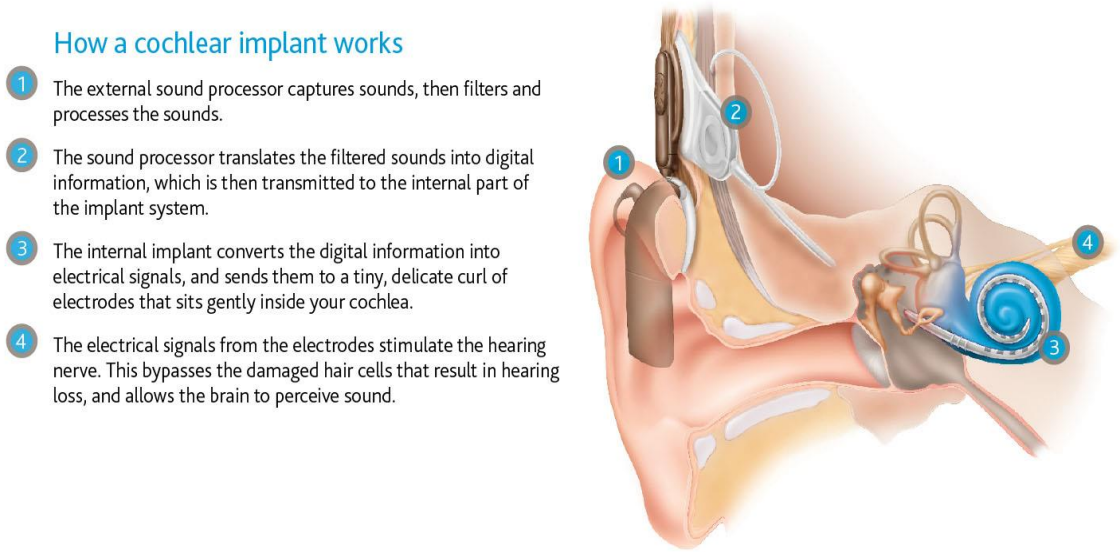

Figure 1: How a cochlear implant works.

The way sounds are processed and presented to the patient is determined by settings in the cochlear implant programming software. Required electrode stimulation levels are measured for each cochlear implant recipient and set to appropriate levels (electric stimulation pathway). In addition, in a Hybrid configuration, the amount of low frequency acoustic amplification to be delivered to the ear via an acoustic component is determined for each individual as a function of their hearing thresholds (acoustic stimulation pathway). An advantage to using a sound processor that combines the two forms of amplification (electric and acoustic) is that it can be done in a manner that coordinates each input for the individual patient's needs (as opposed to a current practice of putting a separate in-the-ear hearing aid in the cochlear implant ear for those patients who retain acoustic hearing sensitivity post-operatively). The stimulation levels and other adjustments are measured prior to turning on the external sound processor.

Some cochlear implant systems, including the topic of this submission, have a remote control that allows the recipient or caregiver to make minor adjustments or monitor the status of the sound processor without removing or touching it.

2 Overview of the Hybrid L24 Implant System

Cochlear Limited is the manufacturer of a series of cochlear implant models that are designed to provide useful hearing to individuals with sensorineural hearing loss ranging in degree from moderate to profound, for low-frequencies, and profound for high-frequencies. This PMA supplement requests approval to introduce a new cochlear implant system to Cochlear's family of marketed implants. The new cochlear implant will be known as the Cochlear™ Nucleus® Hybrid™ L24, hereafter referred to in this submission simply as the Hybrid L24 or the Hybrid implant system. The Hybrid implant represents a modification to the Cochlear™ Nucleus® Freedom implant approved under P970051/S028. The external components of the Nucleus 6 Sound Processor (CP910 or CP920) will be used with the Hybrid implant. Also utilized with the Nucleus 6 Sound Processor with the Hybrid implant system are the CR210, CR220, or CR230 Remote Assistants. Custom Sound Suite v4.0 programming software will be used to program the Hybrid implant. Custom Sound Suite software and the Nucleus 6 Sound Processor System are currently under review in PMA supplement P970051/S096 for use with other implants in the Cochlear family of marketed implants.

The Hybrid L24 implant simply adds a new electrode array to the Nucleus Freedom (model CI24RE) implant receiver/stimulator assembly, and a change in indications for use that allows for a patient population with more low-frequency residual acoustic hearing preoperatively than current Nucleus cochlear implant systems. This is because the shorter Hybrid L24 electrode array is intended to provide a greater possibility of retaining aidable low-frequency hearing postoperatively than conventional long-array electrode arrays.

The Hybrid L24 implant is the result of more than a decade of research by the manufacturer, Cochlear Ltd., into development of an electric-acoustic[1] (EAS) implant system to address the needs of those individuals who demonstrate residual low-frequency hearing sensitivity, but who have severe to profound sensorineural hearing loss at higher frequencies. The device that is the subject of this submission, the Hybrid L24 implant system, was designed specifically for this population. The Hybrid implant system provides access to the benefits of high-frequency hearing via electric stimulation like a conventional cochlear implant, but also is designed with the intention to preserve, when possible, an aidable level of low-frequency hearing sensitivity. If approved for marketing, the Hybrid system would represent the first truly integrated electric-acoustic solution available in the United States for this population of patients with residual low-frequency acoustic hearing but severe to profound sensorineural high-frequency hearing loss.

The Hybrid L24 implant system, like all cochlear implants, includes both implanted and external components. The implanted components of the system are:

- Nucleus Freedom (model CI24RE) cochlear implant receiver/stimulator assembly
- Hybrid L24 electrode array

The receiver/stimulator assembly of the Hybrid L24 implant is identical to that of the Nucleus Freedom cochlear implant that is approved under PMA supplement P970051/S028. However, the Hybrid intracochlear electrode array is different from the conventional long electrode arrays currently available for use with Nucleus implants (the ST [Straight] or CA [Contour Advance]). The Hybrid L24 electrode array is shorter and thinner than Cochlear's conventional cochlear implant arrays, with a goal of trying to preserve a useful level of low-frequency acoustic hearing for the target population by leaving the apical region of the cochlea, which mediates low frequencies, intact.

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[1] Note that some publications refer to electric-acoustic stimulation as "electroacoustic" but because this term has a different meaning in hearing aid measurements , it can be confusing. For this reason, Cochlear believes the term "electric-acoustic stimulation" is preferred.

The external components of any cochlear implant system include a sound processor, transmitting cable and coil. Due to the fact that the clinical trial was completed over a period of 5 years, the Freedom for Hybrid Sound Processor used in the IDE study is no longer being marketed or produced, having been replaced by newer but equivalent technology in the form of the Nucleus 6 Sound Processor. After the Freedom sound processor, Cochlear developed and marketed another newer generation sound processor, the Nucleus 5 (model CP810; Approved under P970051/S049). However, the Nucleus 5 Sound Processor does not have the capability to be run in a Hybrid mode because it does not incorporate an Acoustic Component for acoustic amplification in the low-frequency region where many of the Hybrid L24 patients have residual hearing sensitivity. In contrast, Cochlear's newest generation cochlear implant sound processor, the Nucleus 6 (currently in review under P970051/S096 for use with Cochlear's other models of implants) does have Hybrid capability via an Acoustic Component. Therefore, the newest technology Nucleus 6 Sound Processor system will be used as the external component of the Hybrid L24 Implant System instead of the older Freedom Hybrid Sound Processor that was used in the IDE clinical study.

Specifically, the external components of the Hybrid L24 system that Cochlear wishes to market are:

- The Nucleus 6 (model CP910 or CP920[2]) Sound Processor and coil/cable with battery module and accessories (to replace the Freedom Hybrid sound processor used in the IDE study)
- The model CR210, CR220, and CR230[3] Remote Assistants (the Freedom Hybrid sound processor used in the IDE study did not have remote control capability)

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[2] The CP920 is smaller than the CP910 because it lacks an accessory connector, but is otherwise equivalent.

[3] The CR210 and CR220 are both remotes for CI recipients, with one offering more extensive functionality than the other, but the CR220 is only for clinician use intraoperatively.

- Custom Sound Suite v4 programming software (the Freedom Hybrid sound processor used in the IDE study used Custom Sound Suite v3

The components of the Hybrid L24 Implant System are described in detail in Volume 2 of this submission. Bench testing data showing functional equivalency of the previous generation Hybrid Freedom Sound Processor used in the IDE clinical study and the newest generation Nucleus 6 Sound Processor is summarized in Volume 3 of this submission.

3 Proposed Indications for Use

The Nucleus Hybrid L24 implant system is intended (indications for use) for the following individuals:

- Patients 18 years or older who have residual low-frequency hearing sensitivity and bilateral severe to profound high frequency sensorineural hearing loss, and who obtain limited benefit from bilateral hearing aids.
- Typical preoperative hearing loss of candidates ranges from mild to moderate hearing loss in the low frequencies (thresholds no poorer than 60 dB HL at $\leq$ 500 Hz), and from 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.

For patients with post-operative residual low-frequency acoustic hearing, the Nucleus 6 sound processor has an acoustic component that fits into the concha and canal of the outer ear.

A cochlear implant is contraindicated for individuals with the following conditions:

- Deafness due to lesions of the acoustic nerve or central auditory pathway
- Active middle ear infections
- Absence of cochlear development

- Tympanic membrane perforation in the presence of active middle ear disease

4 Background

4.1 Hybrid L24 Marketing History

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4.1.3 Global Complaint Reports

Cochlear's global complaint and adverse event (AE) reporting system was examined for reports regarding the Hybrid L24 Implant System that occurred globally[5] through December 31, 2012 (the same timeline as for the most recent sales figures reported above in Section 4.1.2). This examination revealed six reportable adverse events for the commercially marketed Hybrid L24 system, as described below. All final reports were forwarded to the relevant Regulatory body(s).

- May 2010, Germany: The implant surgeon reported that an electrode array received from the manufacturer was labeled on the box as a Hybrid L24 array, but appeared be a different electrode array. A manufacturer's investigation concluded that the array was in fact not a Hybrid L24, but rather the SRA research array (now known as the "Slim" and used on the commercial CI422 cochlear implant model). The investigational findings were reported by Cochlear to the Competent Authorities in Germany, Italy, and France, and a CAPA was opened to prevent recurrence of this problem.
- July 2011, Australia: A Hybrid L24 was explanted reportedly due to loss of residual hearing and poor performance.
- October 2011, Australia: A Hybrid L24 was explanted due to short circuit of electrodes 5 and 6, and deteriorating patient performance.

[5] Excluding subjects involved in the clinical trial studies in Europe, Australia, and the United States as those events are reported elsewhere (under Relevant Unpublished Data'.

- March 2012, Australia: A Hybrid L24 was explanted due to loss of all usable residual hearing and the surgeon's decision that the patient would do better with a conventional, longer array. The patient had shown a steady decrease in hearing loss over a 4 year period with an accompanying deterioration in speech recognition scores. The patient was reimplanted with the Nucleus CI24RE implant with Contour Advance electrode array.
- December 2012, Australia: A Hybrid L24 was explanted due to loss of residual hearing preventing use of the Acoustic Component, along with a decrease in speech recognition performance.
- December 2012, Venezuela: Patient had a facial paresis after a Hybrid L24 implantation, but function fully recovered following treatment with oral steroids by 6 months after surgery. Patient reportedly did not like his implant and complained that he only heard high-frequency noises, even though his implant hearing thresholds were reportedly in the 30 to 35 dB HL range.

4.2 Alternative Treatment Options

Patients who present to audiology clinics with the configuration of hearing loss that is proposed for the Hybrid L24 Implant System currently have few therapeutic options available. These patients can choose to do nothing, but the absence of audible mid- to high-frequency sounds will make communication with others difficult, especially when listening in background noise. They can choose to learn speech reading, but it is well known that less than about a third of sound distinctions are visible, even for the best lip reader. They can choose to use assistive devices that are available for deaf patients and to learn sign language, but this is not a population that is familiar with the Deaf Community, and sign language does not allow them to communicate with the broader hearing population. Therefore, the most commonly chosen treatment for patients meeting the Hybrid L24 system indications is the use of conventional air-conduction hearing aids.

Unfortunately, while without intervention these patients experience significant communication difficulties, they typically report a high level of dissatisfaction with amplification and perform quite poorly with conventional hearing aids [e.g. 6]. This is primarily due to an inability to achieve adequate gain for audibility of soft speech sounds that occur in the higher frequencies, even with the highest power hearing aids. Even if some useable amplification is achieved, however, there are often significant problems with acoustic feedback (whistling or "squealing"), a very limited listening dynamic range (the range between audibility and either the patient's loudness discomfort level or the maximum power output [MPO] of the hearing aid), and substantial signal distortion caused by clipping or compression output limiting in high-gain amplifiers. As a result, audiologists may choose to fit these patients by supplying only low-to-mid frequency amplification, but then the patient is left without the high-frequency phoneme energy that is crucial to speech understanding (especially in background noise), and must resort to speech reading in an attempt to "fill in the gaps" of the missing high-frequency sounds. Patients who are candidates for the Hybrid implant often receive insufficient benefit from hearing aids, with poor speech recognition scores due to loss of perception of important high-frequency speech sounds such as fricatives, affricates, and sibilants (e.g. /s/, /f/, /sh/).

High- to low-frequency transposition (shifting) hearing aids have also have been tried for some patients in this population, but outcome studies have not shown very good results [e.g. 7,8]. Further, many patients that fall within the proposed Indications for Use for the Hybrid L24 implant are not candidates for one of these special purpose hearing devices by virtue of having insufficient mid-frequency hearing. Thus, the Hybrid implant system

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[6] Turner, C (2006). Hearing loss and the limits of amplification. Audiol Neurotol, 11(Suppl 1): 2-5.

[7] McDermott, H, Dean, M (1998). Speech perception with steeply sloping hearing loss: Effects of frequency transposition. Br J Audiol, 24(6): 353-361.

[8] Robinson, J, Stainsby, T, Baer, T, Moore, B (2009). Evaluation of a frequency transposition algorithm using wearable hearing aids. Int J Audiol, 48(6): 384-393.

represents a new option that is expected to be successful for this patient population that has shown relatively limited success with the treatment options used to date.

4.3 Relevant Published Literature

A review of the literature was conducted using PubMed Online. Search criteria included the terms "electroacoustic stimulation", "hybrid cochlear implant" and "hearing preservation cochlear implant" in articles published from 2004 through 2013. The last 10 years were selected as they are representative of present day research.

4.3.1 Electric-Acoustic Stimulation (EAS) with Cochlear Implants

The newest treatment option to be explored for patients with severe to profound mid- to high-frequency hearing loss is that of the Hybrid, or combined electric (implant) and acoustic stimulation (amplification) approach. A review of the published peer-reviewed research literature on the topic of electric-acoustic stimulation (EAS) was accomplished using PubMed as a search engine and restricting the literature dates from 2004 to 2013. The reason that the literature review was focused on articles published over the last 10 years is that these research studies are believed to better represent current technology and surgical practices in cochlear implants. Further, included were only those studies with subjects aged 18 and older (studies using only young pediatric subjects were not included because this submission proposes an indication for use of 18 years of age or older). The literature thus identified is summarized in the following and, for the Agency's convenience, copies of key referenced articles most pertinent to the topic of this PMA can be found in Volume 25 of this submission, in order alphabetically and chronologically by the first author. Included in the publications are also review articles on the electric-acoustic stimulation literature by Talbot and Hartley (2008), von Ilberg et al. (2011), and Incerti et al. (2013).

Cochlear and the two other major cochlear implant manufacturers (Med-El and Advanced Bionics) have all developed specialized electrode arrays intended to provide electric-acoustic stimulation. Med-El developed their Flex electrode array models, with the Flex EAS specifically designed for this purpose. More recently, Advanced Bionics introduced the MidScala electrode array, with advertisements indicating it is designed to preserve

hearing/cochlear structures. Both are marketed in Europe, but to date neither has been approved for marketing in the United States.

It is important to realize, however, that the use of acoustic stimulation ancillary to electric stimulation has been used for some time by clinics in the United States with any cochlear implant recipient in whom adequate residual low-frequency hearing sensitivity has been maintained postoperatively. This is possible because even some recipients of cochlear implants with conventional long electrode arrays show enough residual low-frequency hearing sensitivity to receive some benefit from amplification in the implant ear. What will be seen in this literature review, however, is that fewer patients maintain hearing with a conventional long electrode array compared with the shorter and thinner Hybrid L24 electrode array that is the subject of this submission. Further, patients who are candidates for conventional cochlear implants have less low-frequency hearing to begin with compared with candidates for the Hybrid L24, and thus may receive less benefit from acoustic amplification.

When U.S. clinicians are confronted with a patient with residual hearing post-implantation, at this time they only have the option of using an off-the-shelf power ITE hearing aid placed in the implant ear along with the cochlear implant sound processor. A problem with this approach (as discussed on section 4.3.4) is that the ITE is then not optimized for use with the CI as there can be excessive crossover of the acoustic amplification intended for the low frequencies with the electric stimulation of the mid and high frequencies, causing problems. Med-El has marketed in Europe an EAS sound processor (Duet, and more recently the model Duet 2) that provides EAS combined in a single processing unit, but it is not yet available on the US market. The Nucleus 6 Hybrid Sound Processor that is the external unit for the Hybrid L24 implant system coordinates EAS stimulation in a single unit in order to provide the best possible stimulation fitted to each individual patient's need.

It is also very important to keep in mind that hearing preservation is not the end goal per se of these devices. Rather, the primary goal is improved performance by the patient in their everyday listening environment, whether or not residual hearing is maintained in the implanted ear. As is shown in the IDE clinical study summary, the Hybrid L24 implant

provides patients with an option that is more likely to retain usable degrees of residual hearing than a conventional CI would. However, even those subjects who do not receive benefit from acoustic amplification in the implant ear due to loss of residual hearing post implantation may still perform better in their everyday listening condition with the Hybrid implant and a contralateral hearing aid than they did with preoperative bilateral hearing aids. The everyday listening configuration for these latter patients is electric-alone stimulation in the implanted ear, and a hearing aid on the unimplanted ear, a configuration that is commonly called bimodal device use. Many conventional CI recipients use a hearing aid in the unimplanted ear. Research literature on bimodal device use, also reviewed herein, indicates that combining the acoustic and electric stimulation across ears rather than within an ear also typically results in better performance than with hearing aids alone. The brain is able to use the low-frequency acoustic input in one ear combined with the mid-to-high frequency electric input to the other ear. Occasionally, a Hybrid recipient who loses residual hearing in the implanted ear chooses to be explanted and reimplanted with a conventional long array. The literature on these latter patients, as summarized in this volume, shows that good performance can still be obtained following reimplantation.

To facilitate the following review, Table 2 on the next page provides a comparison of approximate length, insertion, and other parameters of standard commercial electrode arrays from the three major cochlear implant manufacturers, compared to the Hybrid L24 electrode. The Hybrid L24, if approved, would represent the shortest marketed electrode length to date[9]. Other factors such as the width and flexibility of the electrode arrays, whether or not it is pre-curved, and the angle of insertion, have also been touted for various models as possibly important factors in determining preservation of the integrity of cochlear structures and, hence, potential preservation of acoustic hearing.

In this section of the volume, the published literature is reviewed for the following topics:

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[9] Other than Med-El's "compressed" electrode, but that electrode is intended for cochlear ossification cases, not for EAS stimulation in patients with a normal cochlear structure.

- Residual hearing preservation and EAS with conventional, long electrode arrays either fully or partially inserted into the cochlea,
- Development of new types of electrode arrays and sound processors that are specifically intended for EAS stimulation,
- Publications pertaining to Nucleus Hybrid implant systems,
- Explantation of a Hybrid electrode array and reimplantation with a long electrode array for patients who had lost residual hearing and whose performance with the Hybrid L24 did not meet expectations,
- Use of acoustic and electric stimulation in users of bimodal devices.

4.3.2 Hearing Preservation/EAS with Medium and Long Electrode Arrays

In order to use a combined electric-acoustic stimulation (EAS) approach with a cochlear implant patient, there must be adequate residual acoustic hearing in the low frequencies so that amplification will provide audible low-frequency sensitivity, while the cochlear implant will provide mid- to high-frequency sensitivity for sounds. It is generally agreed that full insertion of standard long electrode arrays (Cochlear's Straight, Med-El's Standard, and Advanced Bionics' HiFocus 1j) often results in the loss of acoustic hearing sensitivity in a majority of patients. Loss of residual hearing sensitivity post implantation is due primarily to direct trauma to the inner ear, which will be more widespread with a conventional long array, but there may also be an immune reaction in the cochlea triggered by the implant that can lead to delayed decreases in acoustic hearing[10].

[10] This is one reason that some surgeons choose to give steroids or other pharmaceuticals prophylactically at the time of surgery or shortly after, but it is not clear at present if this practice results in better acoustic hearing outcomes post implantation. See Dinh & Van de Water (2009), Souter et al. (2012), and Barriat *et al*. (2010).

[redacted]

Nevertheless, it is also well known that at least some patients implanted with certain conventional cochlear implant electrode arrays do show some degree of preservation[11] of residual low-frequency hearing sensitivity after implantation, as illustrated in the studies reviewed in this section. With conventional electrode arrays currently on the U.S. market, this appears most likely to occur with Cochlear's pre-curved perimodiolar Contour Advance electrode array, Med-El's Medium or Flex electrode arrays, or with partial insertion of longer arrays.

4.3.2.1 Cochlear Nucleus Cochlear Implants

A number of studies on hearing preservation with conventional cochlear implant electrode arrays have evaluated Cochlear's Nucleus implant with the Contour Advance (CA) electrode array because the Softip and AOS (Advance-Off-Stylet) technique for insertion of the CA electrode array are believed to be less traumatic to the cochlea than the Straight electrode array. The CA electrode array also has slightly less insertion depth than other conventional long electrode arrays (see Table 2), so it is expected to leave more of the apical region of the cochlea relatively undisturbed.

For example, Fraysse et al. (2006) reported results of a multicenter European study of 27 adult subjects implanted with the CA electrode array. Of these, 26% reportedly showed hearing preservation within 20 dB of preoperative level at 250 Hz, and 19% achieved this degree of hearing preservation at 500 Hz. Of the 12 subjects in whom the "soft surgery" protocol with AOS technique was more strictly followed, 50% showed < 20 dB decrease in hearing thresholds at 250 Hz and 33% at 500 Hz. Median threshold decreases were 40

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[11] It should be noted that the term 'preservation' is often used loosely in the literature to mean that at least some measurable acoustic hearing remains. Preservation in this context doesn't necessarily imply that functional acoustic hearing remains, though it may be consistent with a less traumatic insertion technique and/or electrode array designs.

dB averaged across 250 and 500 Hz for the entire group, and 23 dB for the "strict" surgery group. Ten of the 27 subjects reportedly had enough preserved low-frequency hearing to receive at least limited benefit from acoustic amplification of the low frequency region in the implant ear, in addition to the electrical stimulation.

In two publications, James et al. (2005, 2006) also reported results from multicenter European studies on hearing preservation with AOS technique and the CA electrode array. In the 2005 study, median increases in thresholds for the 12 subjects were 27 dB at 250 Hz and 33 dB at 500 Hz, including two subjects who showed complete hearing loss at these frequencies. Six of the 12 subjects were able to receive some amount of benefit from acoustic amplification in addition to the implant. In the 2006 study, all 10 subjects had preoperative hearing thresholds < 60 dB HL at 250 and 500 Hz. Of these, seven showed some low-frequency hearing preservation post-implantation and were able to use amplification in the implant ear with some limited success.

Balkany et al. (2006) reported that 32% of 28 severely to profoundly hearing-impaired adults had hearing decreases < 10 dB in the low frequencies postoperatively (average 250, 500 and 1000 Hz), and another 36% experienced average losses < 30 dB following implantation. However, these researchers could not demonstrate any evidence of benefit from acoustic stimulation in addition to the electric stimulation in this group of patients, likely due to the limited amount of residual hearing remaining post-implantation. Similar results were reported by Garcia-Ibanez et al. (2009).

Retrospectively comparing residual hearing across patients implanted with a Nucleus Straight, Contour, or CA electrode, Berretini et al. (2008) reported that the greatest hearing preservation occurred with the CA using the AOS technique. Of the patients implanted with the CA, 81.1% were reported to have some degree of hearing preservation defined as a measurable hearing threshold.

Obholzer and Gibson (2011) conducted a large study of 81 subjects, 68 of whom were implanted via the round window with a Nucleus with Straight array, and 13 with a CA

array. These researchers reported that 58 (about 2/3) preserved some degree of residual, mostly low-frequency hearing at 6 months. The mean deterioration in threshold for those with residual hearing was reportedly 15 dB at 500 Hz.

Cochlear's most recent full length electrode array is marketed under the name "Slim" (the developmental name was the "Straight Research Array [SRA]", and this name is used in the published literature). This electrode array is available as the CI422 cochlear implant model (P970051/S064). Although this electrode array is full length, because it has a substantially slimmer diameter some surgeons believe it may cause less trauma to the cochlea upon insertion and thus possibly result in more hearing preservation than a wider diameter array. Briggs et al. (2006) compared use of round window and cochleostomy approaches with a prototype SRA electrode array using human cadaveric temporal bones, and reported that either approach resulted in limited intracochlear trauma. Skarzynski et al. (2010) evaluated insertion of this array into 22 human cadaveric temporal bones compared to insertion of the standard Nucleus Straight (ST) electrode array, and reported that insertion of the SRA produced less intracochlear trauma than did the ST.

In a more recent study, Skarzynski and colleagues (2012) evaluated the Slim (SRA) electrode array in 23 adult implant recipients who had more residual low-frequency hearing than currently FDA-approved for this CI422 implant. The adults were divided into three groups by the degree of low-frequency acoustic hearing (< 50 dB, 50 to 80, >80 dB HL). Speech recognition was found to be significantly improved compared to preoperatively both for listening in quiet and in noise at 4 months post-implantation. The mean score preoperatively was 34.4% for words in quiet, but 61.7% postoperatively. The mean preoperative score for words in noise was 10.6%, but was 46.5% postoperatively. All subjects retained measurable hearing at 500 Hz in the implanted ear at 4 months after the operation. At 13 months, the median increase in low-frequency hearing thresholds was 15 dB for the 15 subjects measured at that interval. Subjects with preoperative low-frequency hearing levels between 50 and 80 dB HL (EAS group) tended to lose more hearing than those with either better or worse preoperative hearing.

A U.S. clinical study is currently underway evaluating safety and efficacy of this electrode array in patients who have more residual hearing than conventional CI candidates (IDE No. G120234).

4.3.2.2 Med-El Cochlear Implants

Med-El has marketed both their "Standard" long-length array and a slightly shorter but still conventional electrode array called the "Medium". Although in the United States, the Medium electrode array is marketed as another conventional electrode array option for those cases where deep insertion is not possible or desired, on Med-El's European website the company has stated that this electrode array is intended to provide greater residual hearing preservation for the low frequencies based on the fact that it is shorter and thus leaves some of the apical region of the cochlea undisturbed upon insertion. A number of studies have evaluated hearing preservation with the use of Med-El's Medium electrode array or partial insertion of their Standard array, and reported some degree of preservation in some subjects. Wilson (2010) provides an overview of some of these studies.

For example, Gstoettner et al. (2004) evaluated 21 Med-El C40+ implant patients (aged 15 to 74 years old) with residual low-frequency hearing, some of whom were implanted fully with the Medium electrode array, and some who were implanted with partial insertion of the Standard electrode array. A less traumatic insertion technique was used and insertion was limited to 18 to 24 mm for both electrode arrays. The authors reported complete (i.e., changes of $\leq$ 10 dB) residual hearing preservation in 13 of the 21 subjects, partial (i.e., at least some measurable hearing) hearing preservation in 5 subjects, and total loss of residual low-frequency hearing sensitivity (i.e., no measurable hearing) in three subjects. Speech recognition testing showed substantial benefit, especially in background noise, with the use of combined acoustic (hearing aid) and electric stimulation in the implanted ear for those cases with retained low-frequency sensitivity.

In a similar study in 2006, Gstoettner et al. evaluated recipients over a longer period of time and reported a slightly lower rate of hearing preservation across 23 subjects.

Gstoettner et al. (2008) reported on a European study examining hearing preservation following implantation and the usefulness of EAS. Eighteen subjects with ski-slope hearing losses were implanted across five centers with Med-El C40+ implants with the Medium electrode array. Electrode insertion was limited to 18 to 22 mm. Corticosteroids were also used during and after implantation because it was thought this would increase the likelihood of preservation. Subjects were initially fitted with a Tempo+ sound processor, with an Oticon hearing aid fitted to the same ear two months later. Results showed that 12 subjects had sufficiently preserved hearing to benefit from EAS, three had some hearing preservation but not enough to benefit from acoustic amplification, and three subjects lost all their hearing. All subjects showed statistically significant benefit on speech perception tests over a period of a year compared to the preoperative condition. Subjective benefit outcomes also showed benefit of EAS.

A study of 42 subjects implanted with full insertion to 28 mm depth with round window "atraumatic" insertion was completed by Skarzynski et al. (2011). At 3 months after surgery, some degree of hearing preservation was reported in 39 of the 42 subjects. The number of patients still showing hearing at a little over a year after surgery was 35. By comparing hearing thresholds in the implant ear to those in the contralateral ear over time, the authors defined "surgery-related hearing preservation" as the ipsilateral ear loss minus loss that occurred in the other ear. Using this metric, no significant additional hearing loss was found in subjects, which was suggested by the authors as indicating that postoperative ipsilateral progressive hearing loss in some subjects was caused by etiology rather than the implant surgery.

In some published studies, hearing preservation has been attempted by using only partial insertion of the longer length Standard electrode array, in order to leave the apical-most portion of the cochlea, which mediates low-frequency hearing, undisturbed. For example,

Kiefer et al. (2004) implanted 14 subjects who had hearing thresholds between 20 and 60 dB HL at and below 500 Hz and < 35% correct aided monosyllabic word scores. Med-El Combi 40+ cochlear implants were used with insertion depths limited to 19 to 24 mm. Nine subjects showed ≤ 10 dB decrease in hearing sensitivity in the low frequencies over time after implantation, an additional three subjects showed decreases of 11 to 20 dB, and the remaining two subjects showed complete loss of hearing sensitivity. Postoperative speech recognition scores with the CI (electric stimulation alone) significantly improved over preoperative performance with hearing aids and many subjects showed additional benefit from use of a hearing aid in the CI ear.

In 2005, Kiefer and colleagues partially inserted a long electrode array into 13 adult subjects implanted with Med-El implants. Some of these subjects received a modified long array that spaced the contacts closer together so that more channels of stimulation were available. Eleven of the subjects showed partial hearing preservation, but all scored higher with the cochlear implant than they had with hearing aids preoperatively. Of the subjects retaining some acoustic hearing sensitivity, 11 scored higher with EAS than with the implant alone for sentences in noise, and four showed no difference. The synergistic effect of using both acoustic and electric stimulation produced quite substantial improvements for some subjects.

Podskarbi-Fayette et al. (2010) implanted 11 adults (aged 26 to 53) and 7 children (aged 8 to 15 years old) via the round window with insertion depth intentionally limited to 18 to 22 mm. All subjects had functional residual low-frequency hearing sensitivity prior to implantation but did not receive adequate benefit from hearing aids preoperatively. Postoperative speech recognition testing was done bilaterally with either natural hearing for the low frequencies or acoustic amplification in this range. At 12-months post-implantation, all subjects except one had retained low-frequency hearing sensitivity and benefitted from the CI relative to preoperative hearing aids. The one (adult) subject who lost residual low-frequency sensitivity after surgery performed better with the CI than preoperatively with a hearing aid.

Skarzynski et al. (2007) also illustrated some hearing preservation in 9 of 10 subjects implanted with partial insertion of a Standard electrode array, with good stability of results up to 1 year after surgery. One of the subjects in this study lost all hearing two weeks after the surgery. Neither of the subjects who lost acoustic hearing showed hearing loss progressing in the non-implant ear, suggesting that the implantation itself is the factor in hearing loss. Eight subjects of the nine with partial hearing preservation were reported to use the cochlear implant combined with their natural residual hearing, while the other used a hearing aid on the implant ear.

Finally, in a study at the University of Kansas Medical School, Prentiss et al. (2010) used a round window approach with Med-El Pulsar CI100 CIs with electrode insertion depths ranging from 20 to 28 mm in an attempt to preserve residual hearing of 18 adult patients (aged 26 to 84). Patients had low-frequency hearing thresholds ranging from normal to severe, and all had preoperative word recognition scores of <40% in the best aided condition. Postoperatively, some degree of residual hearing was preserved in all subjects, but individual results were not reported. No significant correlation was found between insertion depth and degree of residual hearing preservation. Both HINT and CNC word test results showed significant improvement in performance postoperatively for both CI alone and EAS conditions relative to preoperative performance with a hearing aid, but no significant difference was found between the electric alone and EAS conditions, perhaps due to the degree of hearing sensitivity decrease.

Skarzynski et al. (2009) evaluated 19 adult and 9 pediatric patients implanted with Med-El implants and various electrode arrays using a round window surgical technique. Fifteen subjects received a Standard array, 10 received a Medium array, and three received a Flex array. Some of the Flex and Standard arrays were partially inserted (8 channels) rather than fully inserted. It was reported that 26 of the 28 subjects showed some low-frequency hearing preservation immediately after surgery. Over a 1 to 4 year postoperative period, 13 reportedly maintained complete hearing preservation, and 11 showed partial preservation. Looking across electrode arrays, all inserted to about a 20

mm depth, mean hearing preservation was similar. Highly significant improvements were seen with the implant in the recognition of monosyllables.

In 2010, Skarzynski et al. (2010b, 2010c) reported on 95 adult and pediatric patients implanted using their round window technique with Med-El cochlear implants. Medium electrode arrays were fully inserted (N = 31) but Standard (N = 52) or Flex (N = 12) electrode arrays were partially inserted. The authors reported that hearing was preserved in 91% of the adults and 100% of the children, as defined by the authors as a post-operative hearing threshold less than 80 dB HL.

Thus, partial insertion of a full length electrode array has reportedly resulted in at least some hearing preservation. An obvious overall problem with this approach, however, is that only some of the electrode bands will be inserted into the cochlea, thus reducing the number of stimulation channels available. Therefore, in an attempt to provide hearing preservation with a fuller compliment of electrode contacts, Med-El introduced in Europe a "Flex Soft" electrode array, which is the same active length as the Standard, and a "Flex EAS" (also now known as the Flex[24]) electrode array, which is the same active length as the Medium array. The Flex arrays, although still longer length and straight, were designed for less traumatic insertion than the company's other models due to their flexibility and thinner diameter. A main difference between Med-El's Flex electrode arrays and their Standard and Medium arrays is that in the Flex models the five most apical contacts are not paired, and the electrode spacing is reduced. Note that these electrode arrays are being marketed in Europe, but have not yet received FDA approval for marketing in the United States.

Helbig *et al* published two articles using the Flex Soft array (2011a, 2011b). In both these studies it was reported that the Flex Soft resulted in some degree of hearing preservation, and that EAS resulted in improved speech perception relative to preoperative hearing aid use.

In 2009, Gstoettner et al. reported on 11 adult and pediatric patients implanted with the Flex EAS electrode array, nine via a round window approach and two via cochleostomy. Hearing was preserved to some degree in all subjects. In three subjects, initial threshold shifts measured 1-month postoperatively recovered later to some degree, and one of these subjects, who had shown complete residual hearing loss postoperatively was reported to have completely recovered to their preoperative residual acoustic hearing levels by 17 months postoperatively. Overall, there was reportedly a 44.4% "complete" hearing preservation rate, defined as mean low frequency thresholds (125 to 750 Hz) changing less than or equal to 10 dB from preoperative to postoperative measurements. Mean Freiburg monosyllabic word scores measured in seven subjects showed improvement from 9% correct preoperatively with hearing aids, to 48% correct postoperatively with electric stimulation only, to 65% postoperatively with combined electroacoustic stimulation. Mean HSM (Hochmair-Schulz-Moser) sentence scores in quiet were 30% aided preoperatively, 75% postoperatively with the cochlear implant alone, and 79% for EAS stimulation. Mean HSM sentence scores in noise were 10% aided, 42% with the cochlear implant, and 50% with EAS stimulation. Substantial individual variability was seen.

Fourteen Med-El cochlear implants with Flex EAS array were implanted using a cochleostomy approach in 13 subjects (adults and pediatrics) in a study by Bruce et al. (2011). No speech recognition scores were obtained, but hearing threshold measurements showed that low-frequency acoustic sensitivity was preserved to some degree in 12 of the cases. Arnolder *et al* (2010) reported similar results with the Flex EAS, and Usami et al. (2011) also reported hearing preservation in one subject with the Flex Soft array and four subjects with the Flex EAS array. Most recently, Erixon et al. (2012) reported high rates of residual hearing preservation in 21 subjects with Med-El implants and Flex EAS (N = 20) or Flex Soft (N = 1) electrode arrays. Some of the subjects showed some low-frequency hearing threshold decreases but there was no incidence of total hearing loss.

In 2011, Gstoettner et al. evaluated subjective impressions of 23 patients with a Flex EAS electrode array by using the APHAB questionnaire. They reported significant improvements in EAS postoperatively compared to the results measured preoperatively with hearing aids. After an initial drop in threshold levels, residual hearing was stable and the results suggest that even if some hearing is lost postoperatively there can be subjective benefit.

In a recent investigation, Tamir et al. (2012) retrospectively examined 19 ears of 15 adults implanted with the Flex EAS (N = 4) or Flex Soft (N = 15) arrays. They reported that both arrays resulted in some hearing preservation with no notable difference between the arrays (possibly due to the small n for Flex EAS), although acoustic hearing was reported to deteriorate after surgery. The mean low-frequency threshold was 55 dB HL before surgery and 81 dB HL after surgery with similar standard deviations.

4.3.2.3 Across-Manufacturers Comparisons and Summary

A number of studies have also examined patients implanted with electrode array models across the different manufacturers for examination of hearing preservation. For example, DiNardo et al. (2007) examined 40 adult and pediatric patients with measurable preoperative hearing who were implanted with devices from Med-El, Cochlear, Advanced Bionics (HiFocus), or MXM (Digifocus), and reported low-frequency hearing preservation in 35% of the subjects, some loss of hearing in 45%, and complete loss of hearing in 20%. These authors did not note any significant differences based on manufacturer or model.

In a retrospective case review, Novak et al. (2007) examined performance in nine patients implanted with different CI models with the electrode array fully inserted: Nucleus 24

implant with Straight or Contour[12] electrode array, or AB HiFocus cochlear implant. These subjects had steeply sloping hearing loss with low-frequency residual hearing outside of the FDA-approved criteria. None of these nine subjects showed postoperative residual hearing in the implant ear, but the seven subjects who had postlingual onset of hearing loss showed significantly improved scores with the implant compared to a preoperative hearing aid. For two subjects who had congenital onset of hearing, the CI improved aided hearing thresholds but not speech recognition.

Soda-Merhy et al. (2008) compared hearing preservation when using conventional electrode arrays from Cochlear (Nucleus 24 with Straight, Contour, or Contour Advance arrays), Med-El (Combi 40+ with Standard array), and Advanced Bionics (90K Focus with 1j array). No significant difference in hearing preservation was found across the different electrode arrays and implant models. However, the degree of preoperative hearing sensitivity was not reported in this study, so it is unknown if ceiling effects may have been a factor in the results.

Also in 2008, Adunka et al. examined the effect of having preoperative residual hearing on speech perception after implantation in 29 recipients of Med-El, Nucleus, and Advanced Bionics cochlear implants. An additional 21 implant users who did not have residual hearing were matched for age and duration of hearing loss to act as controls. The authors found no significant difference in performance between the groups, but the degree of benefit was less for the group with preoperative hearing only because their scores were better preoperatively than the group without preoperative residual hearing.

In a retrospective analysis of 550 adult and pediatric patients implanted with various cochlear implants across the three major manufacturers from 1992 to 2008, Piotrowska

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[12] The Contour electrode array was a model approved 2000, while the improved Contour Advance electrode array was approved in 2003.

and colleagues (2010) searched for factors that might impact preservation of residual hearing post-surgery. They believed that their results indicated an advantage to the round window approach over the cochleostomy approach. The only other factor that appeared to effect hearing preservation was age. Changes in postoperative hearing thresholds compared to preoperative at 125, 250, and 500 Hz were significantly smaller for patients implanted before 19 years of age. Other factors that were not found to have an impact included gender, etiology, degree of hearing loss, and type of electrode array.

Derinsu et al. (2011) evaluated subjects implanted in their clinic with CI models across the manufacturers, with all having conventional long electrode arrays. These researchers reported that some degree of hearing preservation was found postoperatively in 87% of 31 patients examined retrospectively. However, the degree of residual hearing was not of a usable degree for acoustic stimulation of the implant ear in these patients; i.e., the degree of loss was beyond aidable because these patients already had severe to profound hearing loss prior to implantation. This points out the importance of evaluating not only the amount of hearing preservation (or loss) seen postoperatively relative to preoperatively, but also whether the degree of postoperative hearing sensitivity is actually adequate for amplification and whether in fact the patients do benefit from EAS.

A large group of subjects were examined by Cosetti et al. in 2013. These researchers retrospectively evaluated files of 128 adults who had been implanted by a single surgeon between 2005 and 2010 at an academic tertiary referral center in New York. A cochleostomy technique and conventional electrode arrays were used. Of the 129, 43 had an Advanced Bionics 90K implant, 56 had a Nucleus Freedom (CI24RE) implant, and 29 had a Nucleus 512 implant. Only 37 of the 129 subjects (29%) were found to have some residual hearing postoperatively at one or more frequencies, but the authors note that this is because patients were included who had significant degrees of low-frequency hearing loss to begin with. If the criteria was tightened to include only patients with more low-frequency hearing preoperatively like Carlson et al. (2011), the hearing preservation rate increased to 50% or similar to that reported by Carlson *et al*. The authors also admit that

a ceiling effect occurred in many patients, in that preoperative hearing thresholds were sometimes so close to profound that a small drop placed them out of range of the audiometer output. Hearing preservation was correlated with younger age at implantation, but was not related to length of hearing loss, cause of deafness, device type, gender, nor preoperative speech performance or low-frequency pure-tone average.

In the Cosetti et al. (2013) study, no correlation was found between residual hearing and performance on a speech recognition task at 3 months or 1 year after implantation. D'Elia et al. (2012) also did not find a relationship between speech perception and preservation of hearing, nor did Balkany et al. (2006) in similar studies.

Looking across the studies of hearing preservation with conventional electrode arrays, it is clear that some patients do show at least some degree of preserved low-frequency hearing sensitivity[13] and of these, some benefit from EAS. Further, the percentage of patients with some degree of hearing preservation has increased with newer surgical techniques and electrode arrays. However, across these studies, the focus is often on the fact that some level of hearing preservation is possible without considering whether or not the level of hearing preservation was sufficient to receive benefit from acoustic amplification. At the same time, regardless of whether hearing was preserved or not, it is routinely reported that statistically significant improvements in speech perception ability are seen with the implant compared with the preoperative aided condition, illustrating the benefits of even electric stimulation alone for patients with severe to profound high-frequency hearing loss.

Not surprisingly, there have also been differences in protocols used across the studies reported above, including the postoperative interval used to evaluate changes in unaided

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[13] Novak et al. (2007) noted that it is important to consider that any patient showing clear signs of progressive hearing loss might best be served by use of a conventional electrode array rather than one designed for preservation of low-frequency hearing sensitivity.

hearing thresholds in the implanted ear. Occasionally, post-operative hearing loss occurs in a delayed time period. However, it appears that if loss of residual hearing is going to occur post-operatively, it can most likely be expected to happen either immediately post-surgery or within the first six months (which is consistent with the primary endpoint for the Hybrid L24 clinical study reported herein).

A design limitation in some studies is the fact that only group mean results are given rather than reporting of each individual's preoperative and postoperative hearing thresholds and speech scores and subject numbers are often small. Further, some studies of conventional implant arrays have used subjects who have very little residual hearing to preserve. Finally, a limitation in comparing results across studies in the hearing preservation literature is that the definition of "partial" or "complete" hearing loss differs across publications. It is also important to note that it is only a relatively small number of patients who retain enough residual hearing in these studies to benefit from acoustic amplification, and these are more likely to be patients who were implanted off-label; i.e., with greater degrees of residual low-frequency hearing than approved under current FDA candidacy criteria.

4.3.3 Hearing Preservation/EAS with Short (Hybrid) Electrode Arrays

In an attempt to provide better EAS results, Cochlear Ltd. has, for more than a decade, researched the use of shorter and thinner electrode arrays to better maintain cochlear integrity and thus provide the possibility for hearing preservation. It can be seen from Table 2 that the Hybrid L24, if approved, would represent the shortest marketed electrode length to date, although it is only slightly shorter in active length than Cochlear's currently marketed Nucleus Contour Advance (CA) array.

Given the difficulties maintaining usable levels of residual hearing with full or medium length cochlear implant electrode arrays, and the fact that partial insertion of electrode arrays doesn't provide the full number of stimulation channels, Cochlear began in the mid to late 1990s to research electrode arrays that were shorter in length than conventional

electrode arrays so that they would not disturb the apical portion of the cochlea that mediates low frequency hearing. Cochlear developed four models of shorter electrode arrays for EAS application, all based on the model CI24R or CI24RE (Freedom) cochlear implant platform. Implants with these short electrode arrays are called "Hybrid" implants because they offer the possibility to use two forms of stimulation (acoustic and electric) simultaneously. Although results from the IDE clinical studies of the first three of these short arrays are described later in this volume (the fourth array developed is the subject of this submission), the following provides a brief history and a review of the published literature pertaining to the Hybrid devices. A review can also be found in Woodson et al. (2010).

4.3.3.1 Publications on the Hybrid S8 cochlear implant

Dr. Gantz from the University of Iowa first proposed a design for a new, short electrode array, which is why some publications refer to the earlier devices as "Iowa/Nucleus Hybrid" cochlear implants. This first design was 6 mm in length, with 6 active electrodes and 2 ground electrodes. Due to its length this earliest model was sometimes called the Hybrid 6[14]. This electrode was only implanted in three subjects in a feasibility study (IDE No. G990155). Results of the feasibility study showed that useful low-frequency hearing and speech recognition performance could be maintained with use of the short electrode array relative to preoperative. However, significant improvements in speech recognition compared to preoperative performance with hearing aid(s) were not observed. Gantz and Turner (2003, 2004) published results from this initial single-site feasibility study begun in 1999 at the University of Iowa.

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[14] Some also refer to the early models of Hybrid electrode arrays simply as "Hybrid S", with the letter "S" designating "short".

Following the feasibility study, the design of the electrode array was then revised to a 10 mm electrode array (still with 6 active electrodes and 2 ground electrodes), which was referred to as the Hybrid S8 (S for "short" and 8 for the total number of electrodes)[15] and was intended to provide electric stimulation to a broader frequency range. Results under a broadened multi-center trial under IDE No. G990155 (n=87) indicated significant improvements in speech recognition in quiet and in noise compared to the preoperative hearing aid condition, and also better music appreciation than typically achieved by traditional CI recipients. This IDE study was closed, but a number of publications appeared in the literature using the data from the study and from additional work done by Dr. Gantz at the University of Iowa. Gantz et al. (2005) reviewed results with the first 21 of the multi-site study subjects as well as some subjects from the University of Iowa who had used the Hybrid S8 over a period of up to 2 years. Results showed that most low-frequency hearing was maintained in all subjects immediately after surgery, but one subject lost hearing 2 ½ months later due to a viral infection. Mean monosyllabic word scores were 69% at 6 months for the 21 subjects in the IDE trial, and 79% for those with longer term use of the device. Speech recognition in noise was better for the Hybrid users than for matched conventional cochlear implant recipients.

Turner et al. (2004) examined spondee word recognition in the presence of background multi-talkers for the Hybrid S8 implant recipients, normal hearing controls, long-electrode array CI recipients, and hearing-impaired patients. The SNR for 50% correct performance was determined with the level of the words held constant and the background talker level varied. Their results illustrated that, not surprisingly, the normal hearing subjects performed best. They were followed by the hearing-impaired subjects with less hearing loss and then the hearing-impaired with greater hearing loss and the

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[15] Also called the Hybrid 10 in some publications, referring to this model being 10 mm long.

Hybrid patients. Long-electrode recipients actually performed the poorest, with an average 4 to 5 dB poorer score than the Hybrid recipients, with some individual Hybrid subjects performing the task at an SNR 15 to 20 dB lower than the best of the long-electrode subjects. The authors noted that these findings demonstrated the substantial potential benefit of preserving and using residual acoustic hearing. Turner et al. (2008) noted that the degree of hearing loss does not seem to correlate to performance as long as sounds can be amplified to audibility with the acoustic component of the Hybrid system. However, in cases of profound or total loss, the benefit of acoustic is lost and the stimulation received is just electric (CI) alone.

Gantz et al. (2006) published results from the clinical study for 19 subjects who had at least 9 months experience with the 10-mm array. Fifteen of the 19 subjects showed significant improvement in recognition of monosyllabic words when listening with the Hybrid implant with a contralateral hearing aid, compared to listening with bilateral hearing aids preoperatively. Notably, two of the subjects who did not show benefit in speech recognition had duration of severe to profound hearing loss of over 40 years, and it is well known that CI recipients with long duration of loss do not perform as well as those with shorter durations of loss. Experience with the Hybrid implant was shown to benefit performances, with improved scores often seen between 3 and 12 months post-implantation, and for some subjects even between 12 and 24 months post. Reiss et al. (2008) showed that some recipients, when they were listening in an electric-only condition (i.e. without any added acoustic information), performed as well as long-electrode array users.

Luetje et al. (2007) reviewed results of 13 Hybrid S8 recipients implanted at their clinical site, reporting that postoperative hearing thresholds were within 10 dB of preoperative in seven of the 13 subjects; however, one of these 7 later sustained hearing loss after an episode of vertigo while flying in an airplane. In the other four cases, postoperative hearing thresholds were within 10 and 30 dB of preoperative, one with hearing loss a week after surgery, two with delayed hearing loss at 2 and 24 months postoperative, and

one with a bilaterally progressive loss apparently not related to the implant. Eleven of the 13 subjects had improved CNC word scores compared to preoperative aided, when listening in Hybrid mode (electric plus acoustic in implant ear). Four subjects showed improvement in BKB sentences in noise testing compared to the preoperative hearing aid condition.

In 2009, Gantz et al. reported on a larger number of subjects from the multicenter study. Results indicated that a majority of the Hybrid S8 subjects received benefit from the device relative to the preoperative hearing aid condition. At the time of this publication, 61 of the 87 subjects had been tested for CNC word recognition and BKB-SIN sentence-in-noise recognition. Seventy-four percent showed improvement in at least one of these metrics, and improvement in both scores was seen for 48% of the subjects. However, 23% (14 subjects) showed equivalent performance to preoperative; that is, the scores were not significantly improved nor significantly decreased compared to preoperative scores, after 9 to 12 months of device use. There was no correlation between benefit and the degree of preservation of residual hearing in the implant ear, possibly due to the fact that some of the Hybrid recipients obtained significant benefit from the electric stimulation alone. Examination of potential predictive factors for performance using multiple regression analysis showed that preoperative CNC scores were positively correlated with post-implantation performance, while duration of deafness was negatively correlated, just as is seen in conventional cochlear implantation. These two factors were found to explain 91% of the total variance in performance for the 14 subjects who were poor performers.

Adunka et al. (2010) compared performances of two matched groups of adult cochlear implant subjects, one group of 10 fitted with the Hybrid implant versus another group of 10 fitted with a conventional long array electrode. Nine of the 10 subjects in the Hybrid group retained useable residual hearing, while none of the 10 in the conventional cochlear implant group did. Preoperatively both groups had similar CNC word scores, but postoperatively the Hybrid group using electric-acoustic stimulation mode showed

significantly better speech scores than the conventional array. Further, when the Hybrid group was tested using electric stimulation alone (the acoustic component turned off), they performed equivalently to the conventional implant group.

In 2010, Turner et al. reviewed study results to date using Hybrid implants with a goal of developing candidacy guidelines for shorter Hybrid electrode arrays versus conventional long arrays. Their review suggested that age and hearing loss degree were predictive factors in the success of the short-electrode approach.

Two studies examined preservation of cochlear structure and function rather than just hearing preservation *per* se. Roland et al. (2008) evaluated insertion of the Hybrid S8 electrode array into human cadaveric temporal bones, reporting that atraumatic insertion was achieved using an appropriate cochleostomy and technique that provided smooth scala tympani insertions. Gifford et al. (2008) used two measures in normal controls and 13 CI recipients implanted with 10 mm (Hybrid S8; N = 7) or 20 mm (MedEl EAS; N = 6) electrode arrays, to assess hearing preservation changes in audiometric threshold and changes in psychophysical estimates of nonlinear cochlear processing (Schroeder phase maskers with various indices of masker phase curvature at signal frequencies of 250 Hz and 500 Hz). Postsurgery the mean threshold elevation was 12.7 dB for the frequency region 125 to 750 Hz. Nine of the 13 had post-implant hearing thresholds that were within 10 dB of pre-implant hearing threshold. Although most subjects retained some degree of residual nonlinear processing function after implantation, only one subject demonstrated a completely normal nonlinear cochlear function postoperatively. The authors concluded that preservation of normal cochlear function in the cochlear apex is common, albeit not common.

Golub et al. (2012) also evaluated psychoacoustic measures in Hybrid S8 recipients with low-frequency hearing preservation 12 to 33 months postimplantation, and compared to those from recipients of conventional cochlear implants. Obtained were measures of spectral and temporal sensitivity, music perception (Clinical Assessment of Music

Perception test), and speech reception in steady-state noise. Results indicated that music perception pitch performance at 162 Hz was significantly better in Hybrid implant users compared with conventional implant controls, and there was a nearly significant difference in speech reception in noise with Hybrid users performing better on average. Neither Schroeder phase discrimination nor temporal modulation detection thresholds showed any advantage for the Hybrid users, but spectral-ripple measurements were significantly better in the Hybrid group. The conclusion of the study was that clinical benefits seen in Hybrid recipients are due to improved spectral discrimination provided by the residual hearing, but that there is no evidence that residual hearing provides temporal information beyong that provided by the electrical stimulation of the implant.

It is interesting that the work of Reiss *et al* (2007, 2008) and Turner et al. (2008) suggest that frequency allocation in the cochlea of Hybrid patients may actually change with experience with the device. In some patients, pitch perception over time can change with implant experience up to 2 octaves or more. The pattern of pitches may be determined in part by the tonotopic mismatch between the original sound frequencies and the cochlear place of stimulation introduced by the sound processor MAP. Turner et al. (2008) found no difference in speech recognition between a mismatched and matched allocation in the MAP. It may be that the loss of useable low frequency and mid-frequency speech information with the shorter electrode but a more normal high-frequency allocation balances out any advantage of more closely matched sound frequency to cochlear place of stimulation.

Dorman et al. (2009) compared word recognition of 47 subjects whose audiograms indicated they were potential EAS candidates; that is, their audiograms preoperatively showed bilateral precipitously sloping high-frequency hearing loss but relatively good hearing at and below 500 Hz, and speech recognition with hearing aids was poor. Twenty-two of the 47 were implanted unilaterally with the Nucleus Hybrid S8, and 25 were implanted unilaterally with full insertion of a conventional longer electrode array (13 with an Advanced Bionics device, and 12 with Cochlear Nucleus devices). Both the

conventional and the Hybrid group had similar low-frequency hearing and speech understanding in the ear contralateral to the implant. Results showed that those with the conventional longer array lost useable hearing in the implant ear. In the Hybrid group, 15 of the 22 had good preservation of low-frequency hearing with a mean loss from preoperative to postoperative of only about 10 dB. Of the Hybrid subjects who lost hearing, three showed the loss 1 to 3 months postoperatively, one subject lost their hearing progressivly in the period between 6 and 12 months postoperatively. The other three hearing loss cases were reportedly not the result of surgery, because one subject lost hearing in *both* ears between 6 and 12 months postoperativly and two lost hearing due to accidents unrelated to surgery. There was a small but significant increase in speech performance when input to the contralateral ear was added to the Hybrid ear. Speech recognition scores were significantly higher for both groups post-implantation compared to preoperative with hearing aids, but the conventional electrode array group had higher scores when stimulation was presented only to the CI ear or when it was presented to both ears. On the other hand, three Hybrid subjects achieved scores of >70% correct in the CI-only condition, which the authors noted might suggest that patients can ”re-map” electrical stimulation at the base of the cochlea for better speech understanding. They also noted that it might be that a different sample of subjects would show more who could re-map well, or that a longer period of time is needed for subjects to be able to re-map, and thus this would bring their results closer in line with other publications.

In another more recent study, Reiss et al. (2012) examined consonant recognition as a function of the number of stimulation channels for Hybrid S8 implant recipients, long-electrode array CI recipients, and normal hearing controls, in quiet and in background noise. Hybrid users were tested with 1 to 6 channels allocated to a frequency range of 1063 to 7938 Hz, long-electrode users were tested with 1 to 6, 8, or 22 channels allocated to 188 to 7938 Hz or 1 to 6 and 15 channels from the basal 15 electrodes allocated to 1063 to 7938 Hz. Normal listeners were tested with simulations of each CI group and condition. Despite the differences in intracochlear electrode spacing for equivalent

channel conditions, all implant subject groups performed similarly for each channel condition and improved up to at least four channels in quiet and noise. Normal hearing subjects consistently performed higher than the CI users. The authors suggested that the limited channel benefit seen for both groups of CI users was potentially not due only to increases in channel interactions as a function of electrode density, but also to other interacting factors such as patient history, location of the stimulation in the base versus apex of the cochlea, and/or a limit on the number of channels that could be processed cognitively. Karsten et al. (2012) examined optimal fitting of EAS devices to experienced Hybrid patients and found that performance was best when there was no overlap or gap between the acoustic and electric stimulation frequency regions.

Localization ability has also been evaluated in patients using a short Hybrid electrode array. Dunn et al. (2010) reported both localization testing results with an 8-loudspeaker array and speech perception in noise results for 11 patients implanted with a short Hybrid array in one ear who also continued to use acoustic stimulation (hearing aids) bilaterally. No significant differences were found in localization ability for bilateral hearing aid use alone versus addition of the electric stimulation to one ear. However, bilateral acoustic stimulation produced better performance than use of the unilateral Hybrid device alone. For speech perception in noise testing, adding the hearing aid to the ear opposite the Hybrid implant produced improved performances. The authors concluded that this study emphasizes the importance of bilateral low-frequency information in localization and speech-in-noise perception.

Music appreciation of the Hybrid recipients was examined by Gfeller et al. (2006). Normal-hearing controls and long-electrode array recipients were compared to Hybrid users on recognition of familiar musical melodies, for sung lyrics as well as instrumental melodies only, and on recognition of musical instruments. For sung melodies, the Hybrid subjects showed no significant difference from the normal hearing listeners (about 70% correct), but scored significantly better than the long-electrode array group (who scored only about 30% correct). For instrumental melodies only, normal hearing subjects

performed the best, followed by the Hybrid group, with the long-array performing significantly poorer. For musical instrument recognition, accuracy depended on the frequency of the instrument such that Hybrids were only significantly worse than the normal for medium to high frequency instruments, but performed well for low-frequency dominated sounds. These results again suggest that the preserved low-frequency residual hearing make an important contribution.

Electrically evoked compound action potential (ECAP) measurements were done by Kim et al. (2010) to examine their relationship to speech perception in 17 Hybrid S8 recipients, and in 22 conventional long array Nucleus Freedom implant recipients. The 17 Hybrid patients were further sub-divided into two groups: one group (N = 8) used the older Hybrid device that was based on the CI24M platform[16], and the other group used the revised Hybrid S8 design that was upgraded to the CI24RE (Freedom) implant platform. ECAP growth functions were recorded using either an interphase gap of 8 or 45 Ks, and then the slope of the growth function and changes in sensitivity with interphase gap were calculated. Each individual subject's measures were compared with performance on tests of word recognition, with the results showing that changes in sensitivity using the two interphase gaps had no correlation with results of speech testing across the Hybrid users. In contrast, for the slope of the ECAP growth functions there were relatively strong correlations to word recognition performance only for the Hybrid users with devices based on the CI24RE platform. The slopes of ECAP growth functions in traditional CI24RE users with long electrode arrays also were significantly correlated with speech performance, but the correlation wasn't as strong as for the Hybrid CI24RE group.

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[16] This platform was used earlier in the Hybrid S8 IDE study and for the feasibility subjects; Later the platform was changed to the current Freedom implant, which was used for the remainder of the IDE study subjects.

Most recently, Gifford et al. (2013) reported on the usefulness of preserved residual hearing in cochlea implantation, for listening in more complex environments. Specifically, 21 English speaking and 17 Polish speaking CI recipients who had acoustic hearing in the implant ear were evaluated. The subjects were implanted with electrodes that varied in insertion depth from 10 mm for Hybrid implant subjects to 31 mm for the Standard Med-El array. The subjects were tested on speech perception tasks including SRT and sentence understanding, for two test conditions: bimodal, and CI plus acoustic stimulation in both ears (Hybrid plus contralateral hearing aid). Testing was accomplished in an 8-loudspeaker environment with speech from one loudspeaker and restaurant noise from all loudspeakers. Another condition simulated reverberation with a time of 0.6 seconds. Results indicated small but significant improvements in performance for the Hybrid plus contralateral hearing aid condition versus bimodal. These results suggest that acoustic stimulation in the implant ear is useful for listening in complex noise environments, probably due to binaural processing of the acoustic stimulus input to both ears. Postoperative hearing thresholds in the implant ear were also correlated with the degree of EAS benefit for speech recognition in the diffuse noise. However, in simulated reverberation, there was no reliable relationship found between measures of audiometric thresholds in the implant ear, and elevation in threshold after surgery, and improvement in speech understanding. The authors proposed that their study supported the broadening of implant indications for use to include patients with more residual low-frequency hearing than currently approved.

In 2007, the 10 mm Hybrid electrode array design was further revised with the addition of 4 active electrode contacts and referred to as the Hybrid S12 with the “S” meaning “short” electrode (relative to conventional models) and the 12 referring to the number of electrodes (10 active electrode contacts and 2 ground electrodes). Thus, this electrode array has the same short design but offers more stimulation channels than the S8. This design is currently being evaluated in an ongoing IDE (No. G070016) and will be further

described herein in the section on related IDE studies. No publications have yet appeared in the literature for the S12 model of Hybrid implant.

4.3.3.2 Publications on the Hybrid L24 Cochlear Implant

In parallel with the development of the Hybrid S12, Cochlear also developed and evaluated an alternative electrode array design under IDE No. G070191. This is the Hybrid L24[17], which is the subject of this PMA supplement. With an active length of about 15 mm, it has 22 active electrodes (plus two extracochlear ground electrodes). It was developed with the intention to provide good electrical stimulation by using a slightly longer length, but short enough that it would still be expected to assist in hearing preservation. The 22 channels provided also were expected to present greater granularity than the shorter Hybrid models that had only 6 or 10 channels. There have been a few published research reports from Europe on the Hybrid L24 implant, which has been marketed there.

Lenarz et al. (2006) was the first to publish an article about subjects using the Hybrid L24. They reported results of a cadaveric temporal bone study of insertion of the L24 electrode array and preliminary results from four early clinical trial subjects implanted with the device. The temporal bone study demonstrated favorable results with minimal trauma upon insertion. Unlike conventional electrode insertion, no basilar membrane perforation was seen. The clinical data showed an up to 40 dB air-bone gap in 2 of the subjects immediately after surgery but this conductive component went away over a few weeks. Good hearing preservation was seen in all subjects. Only one subject had been fitted with the Hybrid sound processor at the time of this report, and that subject showed improved speech recognition performance with acoustic added to the electric stimulation

[17] The "L" meaning "longer" than the short Hybrid electrode arrays, and the 24 consistent with the nomenclature used in the S8 refers to the total number of electrodes (22 intracochlear + 2 ground).

of the implant ear. Further improvement was seen when the contralateral ear was also included in the testing.

In 2009, Lenarz and colleagues at the Medical University of Hannover in Germany published preliminary results of the European clinical trial on the Hybrid L24 implant (described further in the section in the volume on non-IDE clinical trials). Twenty-four patients with high-frequency deafness and residual low frequency hearing (Hybrid group) were implanted, but an additional eight subjects were included who had less low-frequency residual hearing and were similar to conventional cochlear implant candidacy (extended group). The purpose for the extended group was reportedly to examine the Hybrid implant in an electric-alone condition for these patients who had too much hearing loss to benefit from the Acoustic Component. Electrode insertion was via the round window membrane and no surgical complications occurred. One subject was suspected to have had some electrode migration. Hearing preservation data were only available for 17 of the subjects. During the weeks after surgery, air-bone gaps up to 35 dB were seen, but largely resolved by the time of the fitting. Residual hearing was considered conserved in the majority of cases. One subject had a loss of more than 30 dB, but the hearing partially recovered after 9 months. The median loss in all patients was 10 dB in both groups. Patients were able to use their residual hearing postoperatively to the same extent as preoperatively. In the Hybrid mode (electric + acoustic in implant ear), subjects showed a significant improvement of 21% in speech recognition in quiet using the Freiburger monosyllabic word test compared to preoperative scores with a hearing aid. Results on the Oldenburg sentence in noise test also showed significant improvement with use of the Hybrid. Additional improvement was seen in the “combined” mode where the contralateral hearing aid was also added. Finally, duration of hearing loss was found to be inversely related to benefit.

Buchner et al. (2009) reported sentence recognition results and conducted some additional testing on 22 adult Hybrid L24 recipients, many of whom were the same subjects as in the Lenarz et al. (2009) report. Sentence recognition testing consisted of the

SRT in the Oldenburger sentence test in 3 conditions: CI alone (with broad map), hearing aid on contralateral ear alone, and Hybrid mode (CI + acoustic in same ear, with crossover frequency between electric and acoustic adjusted accordingly). Seventeen of the 22 subjects were also tested using HSM sentences at a +10 dB SNR. For a subset of eight randomly selected subjects, the acoustically presented frequency range was limited to 300, 500, and 700 Hz, and speech perception with a single competing talker was measured. This was done to determine the minimal acoustic frequency range that could produce a synergistic effect with the electric stimulation. Results showed that the Hybrid recipients had an SRT of 15.9 dB in the hearing aid alone condition, 10.8 in the CI alone condition (a smaller number indicates better performance), and 3.9 dB when using the Hybrid sound processor for EAS. These differences were statistically significant. A comparable pattern was found for the HSM sentences with a fixed SNR. Results from the additional experiment suggested that very limited residual hearing below 500 Hz is sufficient to produce a significant improvement in speech perception performance in conjunction with a cochlear implant.

Most recently, a temporal bone study was done by Driscoll et al. (2011). Five Hybrid L24 arrays were inserted into cadaveric temporal bones via the round window, and five by cochleostomy. Results were assessed by micro CT scan and revealed that all electrode arrays were inserted into the scala tympani with no tip fold over. The mean insertion angle was 252°. Insertion was easy, producing minimal intracochlear trauma with either technique; however, insertions using the round window followed a more predictable course and more commonly acquired a proximal perimodiolar orientation and less commonly contacted critical soft tissue structures than did the cochleostomy approach.

4.3.4 Combined EAS Sound Processors

In those cases where sufficient/aidable residual acoustic hearing has been retained with any conventional cochlear implant (either full long array or partial insertion), a common practice in recent years has been the fitting of the patient with a hearing aid on the same

ear as (ipsilateral to) the cochlear implant - - usually an in-the-ear (ITE) model type. The cochlear implant sound processor typically used is in a behind-the-ear (BTE) configuration, thus precluding concurrent use of a BTE model of hearing aid. For example, Vermiere et al. (2008) used an ITE hearing aid in the implant ear of four subjects implanted with the Med-El Medium electrode array. Despite overall good performances with the EAS stimulation, these authors concluded, however, that using a separate ITE can cause problems, particularly due to a limited ability to control the overlap between the electric and acoustic stimulation frequency regions.

Helbig and Baumann (2010) also noted additional issues with use of two separate hearing prostheses on one ear, including that it is cumbersome and not very comfortable for the patient, handling of both can be difficult due to the fact that they may use different types of batteries with different battery life, and the fact that many ITEs do not offer sufficient low-frequency amplification for patients with very poor low-frequency hearing thresholds. They note that for all of these reasons, patients may choose to discontinue use of a separate ITE in the implant ear.

The ideal solution for patients with residual hearing sensitivity is a combined sound processor so that both electric and acoustic stimulation can be coordinated. A combined electric-acoustic stimulation system that provides appropriate setting of the crossover frequency between the acoustic (hearing aid) and electric (cochlear implant) sound processing for each individual patient, and delivers both the electrical and acoustic signals in an appropriate, synchronized manner from a single sound processor package precludes the problems identified by Vermiere et al. (2008). Combined electroacoustic (EAS) implant systems have now been designed specifically to address the needs of those individuals who demonstrate residual low-frequency hearing sensitivity with severe to profound sensorineural hearing loss at higher frequencies, including the Hybrid sound processor that is the subject of this submission. However, no combined EAS sound processor system has yet received approval for marketing in the United States.

Med-El has developed a sound processor that combines electric and acoustic stimulation, called the Duet. This electroacoustic stimulation sound processor is intended for use with their Flex EAS electrode array or with a recipient of any model who has residual hearing preservation. Helbig and Baumann (2010) reported on the fitting of 15 subjects with the Duet EAS system. All subjects were reported to have at least partial hearing preservation after implantation with the Flex Soft Electrode array, and a majority chose to use the EAS stimulation from the Duet. It was noted, however, that those subjects who had hearing thresholds (before or after implantation) of more than 55 dB HL at 125 Hz or 70 dB HL at 250 Hz or more than 98 dB HL at 500 Hz rejected the Duet sound processor and chose to receive only electric stimulation.

Lorens et al. (2008) evaluated performance of 11 experienced adult Med-El CI users with residual acoustic hearing and fitted with a Duet, and 22 who did not have residual hearing and received electric stimulation only. The residual hearing subjects were tested in various conditions: CI only, CI plus acoustic on the implant ear (hybrid condition), "best aided" defined as CI plus acoustic on both ears (hearing aid on non-implant ear also), and Duet acoustic only. On speech recognition tests (Polish), the EAS users were found to perform better on monosyllabic words and sentences in quiet and noise than the conventional CI recipients. Not surprisingly, poorest results were found in the Duet acoustic only condition, and best results in the "best aided" and hybrid conditions.

Finally, Polak et al. (2010) put a Duet sound processor on 24 adults who had substantial low-frequency hearing sensitivity after implantation with a Med-El cochlear implant. Subjects had 7 to 52 months experience with their CI and at least one month experience with their hearing aid prior to testing. Fitting of the Duet was accomplished over a week's period with adjustments in the amplification parameters made sequentially and evaluated in different listening environments until best speech performance was achieved. Subjects were tested in the clinic using the same conditions as Lorens et al. (2008). As has been routinely shown across EAS studies, results indicated a synergistic positive effect of acoustic and electric amplification. Striking improvement was seen when acoustic was

added to the implant ear, and a minor additional improvement with addition of a contralateral hearing aid. Only 25% of the subjects benefitted from addition of the contralateral hearing aid and chose to continue wearing it after the study. The authors concluded that acoustic parameters in the EAS sound processor such as low-frequency slope, compression, and frequency range versus the electric stimulation should be carefully set to optimize patient performance.

4.3.5 Hybrid Explantation and Reimplantation

Despite good results in terms of useable hearing preservation with short Hybrid electrode arrays, there are a few patients who lose too much hearing to benefit from acoustic stimulation in the implant ear. Some of these patients choose to listen bimodally and can do quite well in that everyday listening configuration. In a few cases, however, recipients of Hybrid cochlear implants have chosen to have their device explanted and then to be reimplanted with a conventional electrode array due to loss of hearing and/or performance that is not living up to their or their implant team's expectations. Several articles in the published literature have pertained to Hybrid patients who were reimplanted with a long array.

In 2008, Fitzgerald et al. assessed word recognition (CNCs) and pitch scaling abilities in two such patients, 70 and 81 year old males. These subjects had been implanted with the Hybrid S8, but lost their hearing after a few months. They were tested prior to and after being reimplanted with a Nucleus Freedom implant with a full-length array. For these two subjects, speech recognition scores were much better with the longer array than they had been for the Hybrid. Pitch perception was variable and did not show much improvement after reimplantation. In a letter to the editor regarding this publication, Gstoettner and Arnolder (2008b) stated that they believed the best compromise between hearing preservation and good speech outcomes would be to insert a full 360°, corresponding to 18-24 mm so that it reaches the 1000 Hz region, using an atraumatic surgical technique. In their response to this letter to the editor, Fitzgerald *et al*. noted that

studies indicate deeper insertion does result in more trauma to the cochlea, so that there is a tradeoff between having wider electrical coverage and preserving hearing. They also note that there is no guarantee that an electrode located in a specific region of the basilar membrane will actually stimulate neurons tuned to the exact same frequency that causes maximal displacement of that basilar membrane location. They argued that this may be due to place of stimulation varying with stimulus intensity, differences in neural survival patterns, or possibly that place of excitation may be more mediated by the spiral ganglion than from within the cochlea.

Carlson et al. (2012) also reported on successful revision surgery with a long array replacing a short Hybrid S8 array in four patients. All four subjects had experienced delayed post-operative hearing loss following implantation with the Hybrid S8 and upon reimplantation received a Nucleus Freedom or Nucleus 512 cochlear implant with the Contour Advance electrode array. Retrospective chart reviews revealed that all four subjects performed better after the revision surgery on CNC words and BKB-SIN sentences in noise than they had with the short Hybrid electrode array.

Finally, Jayawardena et al. (2012) did a retrospective case study review of 1 adult and 1 pediatric patient with low-frequency residual hearing who had been implanted with the Med-El Flex-28 (adult) or Flex EAS (child), but were subsequently reimplanted (with the same device and array) because of device failures 12 to 18 months after the initial surgery. Both patients were reported to have complete preservation of residual hearing after reimplantation and showed increased benefit. A similar case and outcome were reported by Kamat et al. (2011).

4.3.6 Bimodal Devices Use in Cochlear Implant Recipients

There are many reports of conventional cochlear implant users benefitting from a hearing aid placed in the non-implant ear; so-called “bimodal” stimulation (e.g. Gifford et al., 2007). For those few patients who do not retain any useable residual hearing after implantation with a Hybrid cochlear implant, listening with bimodal devices is a viable

everyday listening configuration. Ideally, adequate residual low-frequency hearing will be maintained so that there is binaural acoustic input in addition to the electric (CI) input to the implant ear. However, the literature on bimodal fittings is promising for these patients and offers a form of combined stimulation. The literature on bimodal stimulation is lengthy, so in the interest of brevity only a few studies will be mentioned here, but see Ching et al. (2006) and Sammeth et al. (2011) for more complete reviews.

A recent study on bimodal benefit (Zhang et al. 2013) summarized the current status of bimodal device use as follows: "In general, the acoustic signal from the nonimplanted ear (A-alone) provides little-to-no open-set speech understanding. The electric signal from the CI (E-alone) typically provides the essential information for speech understanding. However, combining the acoustic and electric signals often brings about the highest level of speech understanding and sound quality (Shallop et al. 1992; Armstrong et al. 1997; Tyler et al. 2002; Ching et al. 2004; Kong et al. 2005; Gifford et al. 2007a; Dorman et al. 2008, Zhang et al. 2010). The additional benefit provided by the acoustic hearing of the nonimplanted ear (acoustic benefit) varies significantly across patients. Some patients receive substantial benefit, with monosyllable word recognition in quiet improving by 20 to 30 percentage points and sentence recognition in noise improving by 30 to 40 percentage points (Gifford et al. 2007a; Dorman, et al. 2008, Helbig et al. 2008; Gstoettner et al. 2006, 2008; Zhang et al. 2010). Other patients receive much less, or even no benefit. There have also been cases in which combining the two signals produced poorer speech-understanding scores than that observed with the CI alone (Tyler et al. 2002; Ching et al. 2004; Mok et al. 2006)."

In the Novak et al. (2007) study of the CA electrode array in nine adults, two of the adults had congenital onset of hearing. These subjects only showed hearing threshold improvement, and not speech recognition improvement like the other seven subjects who had postlingual onset of hearing loss. However, Novak et al. reported that, when these two subjects added acoustic input via a hearing aid placed on the contralateral ear (bimodal devices), improvement in speech performances were seen.

Rader et al. (2013) investigated speech perception performance of patients implanted with either Cochlear, Advanced Bionics, or MedEl cochlear implants who had a heairng aid in the non-implant ear (bimodal stimulation[18]) compared to those who were bilaterally implanted. Mean speech reception thresholds in noise using an OLSA sentence test were significantly lower (better) in the bimodal group than those for the bilateral CI group across three noise test conditions (CCITT, Fastl-noise, and Oldenburg noise). Both the bilateral CI and bimodal user groups showed a significant improvement in performance for a 4-loudspeaker multi-source-noise-field condition compared to a single frontal noise source, which the authors noted signified an advantage from binaural processing in both groups. Although the scores for monosyllable words in quiet were higher in the bilateral CI group, the bimodal group performed better in different complex noise and sound field conditions. Both bilateral CI and bimodal devices users did not benefit from short temporal masker gaps, so the better performance of the bimodal group in modulated noise conditions was explained as an improved transmission of fundamental frequency cues in the lower-frequency region of acoustic hearing.

In the Richard et al. (2011) study, five users of Nucleus Freedom implants who used a contralateral hearing aid were evaluated. Testing was first done in the hearing aid alone condition, then CI alone, and finally in the bimodal condition. Subsequently, low frequency electrodes corresponding to the region of contralateral hearing were deactivated, and subjects were tested again for speech recognition ability and responses on sound quality questionnaires. Results indicated a benefit of the cochlear implant and an additive effect of bimodal listening for sentences in quiet. As expected, performances in the CI-alone condition decreased after apical electrode deactivation. In contrast, however, speech performances in bimodal mode were not significantly changed by

[18] Rader et al. referred to the bimodal stimulation condition as EAS in their article, but the preferred term is bimodal to avoid confusion with Hybrid stimulation (which is more frequently called EAS).

electrode deactivation in quiet or in noise. Questionnaires suggested compensation of partial electrode deactivation by the contralateral hearing. Moreover, the human voice was reported to be significantly less “metallic” than when listening with only the implant. The authors concluded that the results suggested a complementarity of the acoustic and electric cues.

These findings have been echoed in other studies and the literature as a whole supports the daily use of a contralateral hearing aid in any cochlear implant recipient who has substantial levels of hearing in the non-implant ear (see Sammeth et al., 2011). It can be concluded that electric-acoustic stimulation across ears can be used for improved performance when EAS is not viable in an implant ear due to degree of post-implantation hearing loss.

4.4 Related IDE 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 (EAS) 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.

4.4.1 IDE G990155: Hybrid 6 and Hybrid 10

Beginning in 1999, a single-site feasibility study was initiated (approved under IDE G990155) at the University of Iowa involving three subjects implanted with a 6 mm array with 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 through another IDE amendment 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. This stage has been referred to as the 'Phase I trial'. During this phase, 25 subjects received the 10 mm-array, CI24M-based device called the Hybrid S8. 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 under IDE No. G990155 included 87 patients implanted with the10 mm electrode design. The mean age of the subjects was 58.9 years with a range of 19-82 years.

The study objective of IDE No. G990155 was to evaluate the safety and efficacy of the Hybrid system in providing EAS while maintaining residual hearing in individuals who demonstrate significant residual low-frequency hearing and severe to profound high-frequency sensorineural hearing loss. In this single-subject, repeated measures study, subjects were fitted with bilateral hearing aids following surgical implantation of the implant and an adequate healing period. Acoustic only, electric only (CI), and various acoustic + electric modes were measured in the unilateral and bilateral conditions, using open-set standard speech recognition tests (CNC words, BKB-SIN sentences in noise, and HINT sentences in quiet) to objectively assess hearing performance. Subjective data included the APHAB questionnaire and Sound Quality Surveys (SQS). In addition, pure-tone audiometric thresholds were obtained to evaluate the impact of implantation on

residual low-frequency hearing thresholds. Measurements were taken both preoperatively and postoperatively over a period of 12 months.

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 (EAS) 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 results also showed significant perceived improvements for all subscales, and the SQS 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.

The medical/surgical and device-related effects that occurred in this IDE study were consistent with cochlear implantation in general, and not unique to the Nucleus Hybrid cochlear implant. In all, 107 medical/surgical and device-related effects occurred during the study and, out of those, 78 were resolved during the course of the study with no life-threatening, hazardous or permanent side effects. Of the 29 cases that were not resolved before the conclusion of the study, there were:

- 10 cases of complete loss of low-frequency hearing,
- 9 cases of tinnitus,
- 3 cases related to a perceived sound quality problem,
- 2 cases of lightheadedness or vestibular symptoms,
- 2 cases of poor or decreased performance,

- 1 case of taste disturbance,
- 1 case of ear infection, and
- 1 case of scalp pain/tenderness.

Loss of hearing in this IDE study is further analyzed in comparison to the loss of hearing for the Hybrid L24 implant IDE study in Section 5 of this volume.

4.4.2 IDE G070016: Hybrid S12

Although good results were achieved in IDE No. G990155, it was hoped that even better results could be achieved with more electrode contacts/channels. Thus, another short Hybrid array was developed by Cochlear, which was also 10 mm long, but that had more electrodes (12) on the intracochlear array (with two extracochlear). This electrode array, called the Hybrid S12, is currently undergoing investigational study in IDE No. G070016.

IDE approval for G070016 was received in 2008. This investigational device is a modification of the 6-electrode device used in IDE No. G990155 (described above). The modifications included the addition of four active electrodes (a 10-electrode array) 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 cochlea and to enhance quicker sealing of the cochleostomy.

In this single-subject repeated measures study, candidates were assessed in the unaided and aided (i.e., with hearing aids) conditions preoperatively to evaluate their appropriateness for entrance into the study and to establish baseline measures. Postoperatively, acoustic alone and EAS modes are tested in the unilateral and bilateral conditions to evaluate the usefulness of adding the electric stimulation while attempting to preserve low frequency hearing for acoustic stimulation. Speech recognition tests (SRT, CNC words, and AzBio sentences in noise) are being used to assess hearing performance over time (3-, 6-, and 12-months postoperatively), 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 is administered at the 6-month test interval. Subjective testing includes the Speech, Spatial, and Sound Quality questionnaire (SSQ) and a custom Device Use Questionnaire (DUQ) administered at the 6- and 12-month intervals. The primary endpoint of the study for device efficacy is the 6-month evaluation.

As of December 31, 2012, 57 subjects had consented to be evaluated for participation in the study. The subjects range in age from 41-86 years. Of these 57 subjects,

- 1 subject was being screened
- 14 did not meet study requirements during the candidacy evaluation
- 16 were candidates but chose not to proceed with implantation
- 2 subjects were approved as candidates but were not yet implanted
- 24 had been implanted with the Nucleus Hybrid S12 cochlear implant. Of those implanted:
    - 24 subjects have initial activation interval data,
    - 24 subjects have 3-month postactivation data,
    - 23 subjects have 6-month postactivation data(one subject missed the 6 month evaluation due to a scheduling conflict) and;
    - 22 subjects have 12-month postactivation data (one subject withdrew from the study prior to the 12 month evaluation and one subject decided to be re-implanted with a traditional array and did not complete the 12-month evaluation)

Over the course of this multicenter study, 9 sites have received IRB approval; However, 3 sites closed with their IRB prior to implanting any patients. Five sites have implanted patients and one site is still active but has not yet implanted a patient.

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 sub-tests) 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 this study. Loss of hearing in this IDE study is further analyzed in comparison to the loss of hearing for the Hybrid L24 implant IDE study in Section 5 of this volume.

4.5 Relevant Unpublished Data

The fourth Hybrid cochlear implant electrode array developed by Cochlear is the L24, which is the subject of this submission and of IDE No. G070191. 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 long arrays. The IDE clinical study results for the Hybrid L24 study are described in Section 5 of this submission, but there have also been two completed studies of the Hybrid L24 Implant System done outside of the United States. The first was a multi-center European study in support of obtaining the CE mark and the second study was in Australia. There have also been several patients implanted with the Hybrid L24 in Canada, as described further below.

4.5.1 European Clinical Trial

In 2006 Cochlear initiated a multi-center 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 (EAS). The study was conducted in accordance with ISO 14155 and the Declaration of Helsinki. The objectives of the study were: 1) to measure the

preservation of residual hearing in subjects who receive the Hybrid L24 implanted through the round window and 2) to investigate the post-operative performance of the Hybrid subjects in their 'best-aided condition' as compared to their best-aided preoperative performance.

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 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, with 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. It was reported that two subjects withdrew from the study with non-study related illnesses reported and three additional subjects withdrew for non-medical or non-device-related reasons. Subject enrollment began in late 2006 with the final subject completing 12-months follow-up in September 2010. The CE mark was authorized with partial study data, so some sites

enrolled subjects without needing Ethics Committee approval (since it was by then an already approved device). 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.

Group mean and median changes in pure-tone thresholds were calculated for each test frequency at each interval. Those thresholds exceeding equipment limits were accounted for pre-operatively and post-operatively in the analysis section of the report.

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 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 occurred requiring 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.

4.5.2 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 Savia in-the-ear (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 post-operative 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); monaural 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[19] 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 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 condition (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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[19] One subject withdrew at 3-month interval due to Alzheimer's disease

4.5.3 Canadian Hybrid Subjects

The first Hybrid device to be implanted in Canada was the Hybrid S8 under Canada's Special Access regulations. Two devices were implanted in adults (age 52 and 62) in February 2007. While this was not part of a clinical study, audiometric threshold data (air and bone conduction) were provided to the manufacturer at different intervals from preoperative through 12 months of use. Both patients presented with mild-moderate low frequency hearing loss dropping precipitously to profound levels above 750 Hz. Twelve months after implantation with the Hybrid S8 device, one patient had experienced a mean drop of approximately 30 dB in the low frequencies while the second only exhibited ≤15 dB mean threshold decrease below 1000 Hz. One of the patients reported increased tinnitus in the implant ear after surgery. A cortisone regimen was prescribed and the subject was counseled. After twelve months of implantation, the patient reported the tinnitus was still present. No other information is available on these patients.

In 2011 an application was made to Health Canada for approval of the Hybrid L24 for all age groups. The application included European and Australian clinical data in addition to published clinical reports. In parallel, an ITA at a single site was filed with Health Canada and the local Ethics Committee to initiate a study specific to the pediatric population for the Hybrid L24 for potential market release data. Following receipt of the required study approvals, one child (age 11) was implanted prior to notice to the sponsor (Cochlear Americas) of Canadian approval for the Hybrid L-24 that included the pediatric to adult population in its indications for use. At that time it was decided by the site to discontinue study enrollment under the ITA and the study was closed.

For the single child implanted under the ITA, pure tone air and bone conduction thresholds at each ear were obtained from candidacy through 12 months post-implantation. Additionally, CNC phoneme and word scores (quiet) and PBK words in noise were tested preoperatively (aided) and post-implantation at 12-months. The aided CNC word preoperative scores (66% bilateral and 56% ipsilateral) were compared to 12-

month scores with the Hybrid device (64% combined and 57% Hybrid). The PBK words (in noise) were also tested at the same intervals with preoperative scores of 58% (bilaterally aided) and 58% (ipsilaterally aided) as compared to 12 months scores of 54% (combined) and 62% (Hybrid). There were no reported adverse events for this subject.

5 IDE G070191: Clinical Trial of the Hybrid L24 Implant

5.1 Study Synopsis / Abstract

A clinical trial study was conducted on the Nucleus Hybrid L24 implant system from 2007 to 2012 (with long-term follow-up re: acoustic hearing preservation continuing). Fifty subjects with severe to profound high-frequency loss but significant levels of low-frequency acoustic hearing, were implanted across 10 clinical sites. The primary endpoint was 6-month postactivation, with patients listening unilaterally in the "Hybrid" condition (EAS stimulation). On a daily basis, however, most subjects use the Hybrid implant along with a hearing aid in the other ear; i.e., in the "Combined" condition.

Results of efficacy testing revealed: 1) Significant improvements in speech recognition in both the Hybrid and Combined conditions over preoperative performances with hearing aid(s), both for words and phonemes in quiet (CNC test), and for sentences (AzBio) in background noise at +5 dB SNR; 2) Substantial improvements in aided thresholds in the high-frequency range with the Hybrid compared to the preoperative hearing aid, and 3) Positive perceived benefits and satisfaction in most cases, based on questionnaire data. Examination of individual data at 6-months postactivation revealed that ≥ 90% of subjects had a postoperative score equal to or better than their preoperative score in the unilateral, Hybrid condition (i.e., ipsilateral electric and acoustic stimulation), and 100% in the everyday, Combined condition (i.e., ipsilateral electric and bilateral acoustic stimulation). A large majority of subjects showed postoperative improvement on performance outcomes compared to preoperative.

The safety profile in terms of adverse events was comparable to that of conventional cochlear implant models in terms of surgical complications, tinnitus, vertigo, etc., and there were no unanticipated adverse events. Low-frequency acoustic hearing sensitivity was preserved at a level sufficient for amplification use in the implant ear in most, but not all, subjects. Approximately fifty-six percent of the subjects had ≤ 30 dB decreases in low-frequency hearing (averaged over 125-1000 Hz inclusively). Even those subjects who were unable to use low-frequency amplification due to the degree of their postoperative hearing loss still usually showed significantly improved speech perception outcomes compared to preoperative amplification. A few subjects chose to be reimplanted with a long-array electrode due to loss of hearing sensitivity and subsequently lower performance than desired, but most are performing well with their new implant.

5.2 List of Abbreviations and Definitions of Terms

Table 3 contains a list of terms/abbreviations (acronyms) and their definitions, as used in the description of this study, and in the associated attachments to the clinical volume.

Table 3: Terms, acronyms and definitions in the clinical investigations volumes.

Term/Abbreviation	Definition
Acoustic Alone	Pre- or postoperative condition referring to the use of acoustic hearing alone, with or without amplification, ***ipsilateral*** to the implanted ear (i.e., in the same ear as the implant).
Acoustic Component	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

Term/Abbreviation	Definition
	noise for this study.
Best Bilateral Listening Mode	Postoperative listening condition referring to either Combined Mode (defined below) or Bimodal Mode (defined below); assumed to be the Combined Mode unless the subject experienced a loss of residual hearing in the implanted ear.
Best Unilateral Listening Mode	Postoperative listening condition referring to either Hybrid Cochlear Implant Alone or Hybrid Mode (defined below); assumed to be Hybrid Mode unless the subject has experienced a loss of residual hearing in the implanted ear.
Bilateral Acoustic	Pre- or postoperative condition referring to the use of ***bilateral*** acoustic hearing (i.e., acoustic hearing in both ears), with or without amplification.
Bimodal Mode	Use of acoustic hearing, with or without amplification, in addition to electric hearing via a cochlear implant in the ***contralateral (opposite)*** ear.
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. (*Peterson & Lehiste, 1962*).
Combined Mode	Use of acoustic hearing bilaterally, with or without amplification, in addition to electric hearing via a cochlear implant.
CRF	Case Report Form.

Term/Abbreviation	Definition
Nucleus® Custom Sound™	Clinical programming software for Nucleus cochlear implant systems.
Cochlear Implant Alone	Stimulation delivered by the cochlear implant alone.
Hybrid Mode	Combination of acoustic and electric hearing, in the ***same (ipsilateral)*** ear.
ITE	In-The-Ear.
MAP	A program that defines the individualized fitting parameters of recipients for a specific speech coding strategy.
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).

[1.] Consonant-Nucleus-Consonant Test; Peterson, F.E. & Lehiste, I. (1962). Revised CNC lists for auditory tests. Journal of Speech and Hearing Disorders, 27(1): 62-70.

[2.] 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). Ear & Hearing, 33(1): 112-117.

5.3 Investigators and Study Sites

Over the course of the study 10 investigational sites completed at least one surgery. These 10 sites along with the primary investigators/surgeons[20] are listed in Appendix 1, Tab 1, with a designation of how many surgeries were completed at each site.

5.4 GCP Compliance and Ethics

5.4.1 Investigational Review Boards (IRBs)

A list showing the IRB contact information for each site completing at least one surgery under the study protocol can be found in Appendix 2, Tab 1.

5.4.2 Financial Certification/Disclosure Statement

Information concerning the compensation to and financial interests of, or absence thereof, for the primary investigators involved in the clinical study described in this application, including FDA Forms 3454 and 3455 as applicable, can be found in Appendix 3, Tab 1.

5.4.3 Patient Informed Consent Form

A copy of the current patient informed consent form template can be found in Appendix 4, Tab 2.

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[20] The PI for Northwestern, Dr. Fishman, left the institution since the last report. Dr. Micco is now the PI for this site. There has been no new subject enrollment since this change.

5.5 Study Objectives

5.5.1 Primary Objectives

5.5.1.1 Co-Primary Efficacy 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 (i.e., electric + acoustic stimulation in the treated ear) was significantly better than that observed preoperatively with the subjects using Acoustic Alone (i.e., acoustic stimulation alone in the treated ear).

Endpoint:

Comparisons were made between preoperative CNC[21] word scores (Acoustic Alone, ear to be implanted) and 6-month postactivation scores for the treated ear (Hybrid Mode).

Hypothesis:

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

[21] Consonant-Nucleus-Consonant Test; Peterson, F.E. & Lehiste, I. (1962). Revised CNC lists for auditory tests. Journal of Speech and Hearing Disorders, 27(1): 62-70.

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 in the treated ear) was significantly better than that observed preoperatively with the subjects using Acoustic Alone (i.e., acoustic stimulation alone in the treated ear).

Endpoint:

Comparisons were made between preoperative AzBio[22] sentence scores (Acoustic Alone, ear to be implanted) and 6-month postactivation scores for the treated ear (Hybrid Mode).

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.

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. Time to first adverse event was summarized using Kaplan-Meier estimated survival

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[22] 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). Ear & Hearing, 33(1): 112-117.

curves. If any baseline factors were found to be associated with adverse events, an estimate of the risk ratios for any and each adverse event was made, adjusting for those factors.

Hypotheses:

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

5.5.2 Secondary Objectives

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

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

Individual scores obtained at 6 months were compared with those obtained, on the same measures preoperatively, based on binomial comparisons[23].

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[23] Thornton, A.R. & Raffin, M.J.M. (1978). Speech discrimination scores modeled as a binomial variable. Journal of Speech and Hearing Research, 21: 507 518.

5.6 Investigational Plan

5.6.1 Overall Study Design

This study was a prospective, single-arm, multi-center study to determine the safety and effectiveness of the Nucleus® Hybrid™ L24 Implant System. Subjects were implanted at 10 clinical sites in the United States presenting with severe to profound sensorineural hearing loss for frequencies > 1500 Hz, and thresholds no poorer than 60 dB HL for frequencies ≤ 500 Hz. Subjects served as their own controls in all test conditions: Acoustic Alone (ipsilateral to the implanted ear), Bilateral Acoustic, Hybrid Implant Alone, Hybrid Mode (Hybrid cochlear implant + ipsilateral acoustic), Bimodal Mode (Hybrid cochlear implant + contralateral acoustic), and Combined Mode (Hybrid cochlear implant + ipsilateral and contralateral acoustic).

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

In addition to analyses to address the primary and secondary endpoints described above under **5.5 Study Objectives**, additional exploratory analyses involved assessment of the subjects using the Hybrid cochlear implant in the bilateral mode (Combined or Bimodal), reflecting the normal manner in which the device was used on a daily basis. That is, group and individual outcomes for the subjects using the device in the “normal” mode (Combined or Bimodal) at 6 months postactivation was compared with the performance gained in the preoperative Bilateral Acoustic mode.

Further analyses were also made of the low-frequency hearing sensitivity data to adequately describe changes observed postoperatively and to detail how further loss of low-frequency hearing impacted outcomes.

A copy of the current clinical trial protocol can be found in Appendix 5, Tab 2 of this volume.

5.6.2 Selection of Study Population

Qualified subjects were required to meet the following criteria for inclusion and exclusion, respectively:

5.6.2.1 Criteria for Inclusion:

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

5.6.2.2 Criteria for Exclusion:

1) Duration of severe-to-profound hearing loss greater than 30 years.
2) Congenital hearing loss (for the purpose of this study, onset prior to 2 years-of-age).
3) Medical or psychological conditions that contraindicate undergoing surgery.
4) Ossification or any other cochlear anomaly that might prevent complete insertion of the electrode array.

5) Conductive overlay of 15 dB or greater at two or more frequencies, 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.

5.6.3 Efficacy Testing

5.6.3.1 Speech Recognition Testing

5.6.3.1.1 Consonant-Nucleus-Consonant (CNC) Word Recognition Test

The CNC Word Recognition Test (Peterson & Lehiste, 1962) is a validated test of open-set word recognition. The test consisted of 10 recorded lists of 50 monosyllabic words. Two lists were administered in quiet at 60 dBA in the sound field and reported as percent correct for words and phonemes. Subjects were tested using a configuration where the loudspeaker delivering the target speech was at 0º azimuth.

5.6.3.1.2 AzBio Sentence Test in Noise

The AzBio Sentence Test (Spahr et al., 2012) is a validated test that consisted of 33 lists of 20 sentences. Each list includes 5 sentences from each of the 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 at 0º azimuth.

5.6.3.1.3 Speech Reception Threshold (SRT) Test

A Speech Reception Threshold (SRT) test was administered, consisting of a 12-item forced-choice test in which the patient listens for one of 12 target spondees spoken by a female (birthday, drawbridge, eardrum, iceberg, mousetrap, northwest, padlock, playground, sidewalk, stairway, toothbrush, and woodwork). The target stimulus was delivered under the control of custom software in the presence of competing speech (two competing talkers, one male, and one female). The level of the competing signal was adaptively varied depending on the subject's response. That is, the level increased (producing a more aversive signal-to-noise ratio) when a correct response is made and decreased (producing a less aversive signal-to-noise ratio) when an incorrect response was made. In this way, Speech Reception Thresholds could be measured. Speech Reception Threshold was defined as the signal-to-noise ratio (SNR) resulting in 50% spondee recognition. A lower SNR to achieve 50% recognition indicated improvement. In other words, equivalent speech understanding was maintained at a more aversive SNR. For this study, the target stimulus was presented at 60 dBA from a loudspeaker located at 0° azimuth. The competing signal was directed towards the right ear (90° azimuth) or towards the left ear (270° azimuth). SRT was measured as an assessment of speech perception in spatially separated noise in the best-listening modes:

a. contralaterally to the ear to be implanted and,

b. bilaterally.

5.6.3.2 Questionnaires

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

The Speech, Spatial, and Qualities of Speech Questionnaire (SSQ) was used as a subject self-assessment of hearing in everyday life across three categories (speech hearing rating scale, spatial rating scale, and sound qualities rating scale).

5.6.3.2.2 Device Use Questionnaire (DUQ)

An "in-house" designed device usability metric, the Device Use Questionnaire (DUQ), was administered to determine subjective preferences and satisfaction with regards to device use in various listening environments.

5.6.3.2.3 Musical Background Questionnaire (MBQ)

The Musical Background Questionnaire (MBQ) is a self-assessment questionnaire that examines musical training prior to hearing loss, listening habits with hearing aids, satisfaction with hearing aids for music listening, quality of music with hearing aids, enjoyment of musical styles with hearing aids, enjoyment of different instrumental timbres with hearing aids.

The SSQ, DUQ, and MBQ were administered pre- and postoperatively with subjects referencing their everyday listening mode. Copies of the questionnaires can be found as Appendices 6 through 10, Tab 3 of this volume.

5.6.4 Safety Testing

5.6.4.1 Audiometric Thresholds

Unaided audiometric thresholds were obtained for each ear, with insert earphones, using the standard audiometric technique for pure-tone testing. Aided audiometric thresholds were obtained for each ear in the sound-filed 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 125, 250, 500, 750, 1000, 1500, 2000, and 4000 Hz.

Aided thresholds were measured at the following frequencies:

- 250, 500, 750, 1000, 1500, 2000, 3000, 4000, 6000, and 8000 Hz;

5.6.4.2 Adverse Events

Adverse events were reported to the Sponsor via the Adverse Effects form provided to each center. The AE form was filled out at each interval, however, it was a requirement to report Adverse effects as soon as they were known. If the adverse effect was reported by means other than the form, it was requested that the reporting party also complete the form and return to Cochlear Americas. The Primary Investigator was required to verify the completion and accuracy of the adverse effects form after each study evaluation. Adverse effects were reported if observed, even if acknowledged as risk factors in the consent. Adverse effects 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.

5.7 Data Quality Assurance

5.7.1 Training of Centers and Study Personnel

5.7.1.1 Clinical site training

Clinical site training was conducted in an Investigator Meeting format as well as via webinars. All surgeons were trained on the surgical technique through the use of a temporal bone laboratory. Additionally, in an effort to maintain consistent communication throughout the duration of the trial, each site received the biannual report summarizing the clinical trial status as well as monthly status reports detailing site specific information.

The initial Investigator Meeting was held April 12- 13, 2008 following the 10th International Conference on Cochlear Implants and other Implantable Auditory Technologies in San Diego, CA April 10 -12, 2008. Ten clinical sites and 21 attendees (a minimum of one surgeon and one audiologist per site) participated. Topics of the meeting included: In-depth review of the clinical protocol and investigational device, good clinical and documentation practices (GCP), requirements for event reporting and monitoring, and the electronic data capture system, Datalabs. A temporal bone lab was also hosted for the surgeons.

Annual status update meetings on the clinical trial data were conducted:

- October 6, 2009 during the 113th AAO-HNSF Annual Meeting in San Diego, CA. Sixteen clinical trial representatives (15 surgeons and 1 audiologist) were present. Additional topics included surgical technique, reimbursement, and subject accrual.
- September 27, 2010 during the 114th AAO-HNSF Annual Meeting in Boston, MA September 26 – 29. Thirteen clinical trial representatives (12 surgeons and 1 audiologist) were present.

- July 15, 2011 during the 13th Symposium on Cochlear Implants in Children July 14-16, 2011. Nineteen clinical trial representatives (14 surgeons and 5 audiologists) were present.

5.7.1.2 Cochlear Staff Training:

Cochlear staff training was conducted January 9, 2008. Twenty-one monitors were in attendance. Topics of the meeting included: overview of the clinical trial protocol, list of participating clinical trial sites, the monitoring plan, and an introduction to the electronic data capture system, Datalabs.

Additional staff training on Standard Operating Procedures (SOPs) was conducted April 7, 2011 and again August 2012.

5.7.2 Description of CRF and Data Capture Process

Each clinical trial site was provided a Pre-Enrollment 'Candidacy' binder and Subject binder. The Pre-Enrollment binder contained all case report forms (CRFs) necessary to determine candidacy and conduct preoperative baseline testing. Upon subject enrollment, the site transitioned to the Subject binder. The Subject binder contained all CRFs from intraoperative through semi-annual evaluations. The site completed each evaluation and its respective case report form then faxed or emailed the data set to Cochlear Americas. Data entry into the electronic data capture system, Datalabs, was completed by Cochlear staff. Copies of the CRFs are stored in subject files in Cochlear America's locked Central Records office in their Centennial, Colorado location.

5.7.3 Monitoring and Audits

The clinical trial was conducted in accordance with the monitoring plan (found as Appendix 11, Tab 4) and applicable internal SOPs. Prior to site enrollment, each clinical site received a New Site and Site Initiation visit to ensure the facility and staff met the requirements of the clinical investigation, personnel had adequate training including

protocol and Good Clinical and Documentation Practices, as well as completion of all study documentation. Preoperative candidacy data was reviewed prior to each subject's enrollment to confirm proper inclusion or exclusion of that subject according to the study candidacy criteria. Intra- and post-operative data were monitored periodically beginning within the first three months (+/- 30 days) after the Site Initiation visit occurred. A minimum of 30% of source data was verified during periodic visits over the course of the clinical trial. Additional periodic visits were planned every three months (+/-30 days) at all active sites throughout the duration of the trial; however, the plan for these visits could be adjusted accordingly depending upon site compliance and/or rapid versus slow accrual of subjects. The monitoring plan was subject to revision at any time during the trial, should the Sponsor determine that revisions to the plan were necessary. A Study Closure visit is conducted at the conclusion of a site's participation in the study. The Study Closure may be completed in conjunction with the final monitoring visit, as long as all subject follow-up has been completed. The purpose of the Study Closure/final monitoring visit is to ensure:

- All clinical trial data are accurate and complete
- All regulatory documents are finalized and present
- All adverse events have been reported to the appropriate authorities
- All devices, test articles and study supplies have been accounted for and any remaining materials have been returned to the Sponsor

Lastly, the Study Closure visit ensures site compliance with record retention, publication requirements and potential FDA audits.

5.8 Statistical Analysis Plan

A copy of the statistical analysis plan (SAP) can be found as Appendix 12, Tab 5.

5.8.1 Determination of Sample Size

Sample size for this trial was based previous clinical trial data for the CNC word recognition and HINT sentences-in-noise tests.

The mean pre- to postoperative change observed in CNC word scores in previous Hybrid clinical trial (IDE study G990155) data at 6 months was 18.1% (S.D., 24.2%). Under these assumptions with a one-sided test conducted at a type-I error rate of 0.025, the minimum sample size to achieve 80% and 90% power to reject the null hypothesis was found to be 17 and 21, respectively.

The AzBio sentence test is a novel test in cochlear implant studies and there are no historical data on which to base sample size estimates. However, a recent publication by Gifford et al. (2008) and personal communication with the first author suggested that the mean difference and variance scores for the AzBio test should be similar to that of the CNC test. A conservative approach was taken in estimating sample size using data for the HINT sentence materials from the previous Hybrid trial, mentioned above. The pre- to postoperative change observed in HINT scores in that trial was 12% (S.D., 22.5%). Under these assumptions, the minimum sample size to achieve 80% and 90% power to reject the null hypothesis was found to 30 and 39, respectively.

Since a nonparametric test will be used in the event of significant evidence of non-normal outcome data for the co-primary endpoints, a sample size 10% greater than that of a simple paired mean comparison test was calculated due to the expected loss of power with a nonparametric test. Further, to protect against a loss of power due to missing data, an additional 10% increase in the sample size for potential loss to follow-up (assumed to be < 10%) was allowed for. Under these assumptions, the minimum sample size necessary to achieve 80% and 90% power for the two co-primary endpoints was 36 and 47, respectively. The final sample size planned for this trial, 50 subjects, exceeded the minimum requirement for statistical power at 90% to provide further assurance for

adequate statistical power and greater justification for generalizability to the wider clinical population.

5.8.2 Plan for Primary Efficacy Endpoints Analysis

The significance of the mean difference between CNC word recognition scores pre-operatively and at 6 months post-implant will be analyzed using a paired t-test. Specifically, define $D_i = Y_{1i} - Y_{2i}$, for $i = 1,2, \ldots n$, as the difference between the pre-operative and 6-month CNC word recognition score, respectively, for subject i. Then let μ_D be the mean difference across all subjects. The formal null and alternative hypotheses are then as follows:

$$H_0: \mu_D \leq 0$$

$$H_A: \mu_D > 0$$

The level of significance for this one-sided test is 0.025. If there is significant evidence that the assumptions of the t-test do not hold (i.e. $p<0.05$ from a Shapiro-Wilks test of normality), a Wilcoxon signed rank test will be used.

The significance of the mean difference between AzBio sentence recognition scores pre-operatively and at 6 months post-implant will be analyzed using a paired t-test. Specifically, define $D_i = Y_{1i} - Y_{2i}$, for $i = 1,2, \ldots n$, as the difference between the pre-operative and 6-month AzBio sentence recognition score, respectively, for subject i. Then let μ_D be the mean difference across all subjects. The formal null and alternative hypotheses are then as follows:

$$H_0: \mu_D \leq 0$$

$$H_A: \mu_D > 0$$

The level of significance for this one-sided test is 0.025. If there is significant evidence that the assumptions of the t-test do not hold (i.e. $p<0.05$ from a Shapiro-Wilks test of normality), a Wilcoxon signed rank test will be used.

5.8.3 Plan for Secondary Efficacy Endpoints Analysis

No formal hypothesis test will be conducted for the CNC word, CNC phoneme, or AzBio secondary endpoints. Success on the endpoint will be achieved if >75% of subjects meet the endpoint. No type-I error control is required since no hypothesis test will be performed.

5.8.4 Plan for Safety Endpoints Analysis

No formal hypothesis test will be performed. All adverse event rates will be reported as the number and frequency of events with corresponding 95% exact binomial confidence limits and the number of events per patient-time (e.g., events per 10 patient years), and compared qualitatively to previous cochlear implant studies.

Time to first adverse event (including total losses of residual hearing) will be summarized using Kaplan Meier plots. Exploratory proportional hazards regression models will be used to determine whether baseline factors are associated with risk for adverse events over follow-up. Hazard ratios and 95% confidence intervals for these analyses will be cited.

Audiometric data will be summarized at each follow-up time point to assess any changes in hearing sensitivity and to characterize the impact of the procedure on residual hearing.

5.8.5 Handling of Outliers, Drop-Outs, and Missing Data

For primary analyses, missing 6-month postactivation data will be imputed using the last observation carried forward (LOCF) approach. Sensitivity analyses will be performed to assess the robustness of results to different assumptions underlying the missing data.

For both the co-primary endpoints, both a best-case and worst-case analysis will be performed. The most favorable (best-case) and least favorable (worst-case) change in CNC and AzBio scores observed in the complete data will be imputed for the missing values and the data re-analyzed using the full data with the imputed data. Summary

statistics for the resulting mean differences and p-values from the primary hypothesis test will be presented.

5.8.6 Subgroup Analyses

The consistency of the primary endpoints will be examined across subgroups of subjects defined by the following baseline characteristics: gender, race, duration of severe to profound hearing loss, baseline CNC word scores, and previous history of otologic surgical history. Any significant difference between subgroups on endpoints will be explored with additional analyses. Similarly, the consistency of the primary endpoints will be examined across investigational sites by testing for an effect of site in ANOVA model; a site effect with an associated p-value less than 0.10 will be considered evidence of possible variation between sites. Any potential variation between sites in the primary endpoints will be explored by assessing whether or not there are differences in baseline characteristics between subjects at sites that might explain the results.

A specific subgroup of particular interest is subjects with low frequency acoustic hearing loss. To examine these subjects, analyses will be performed on the primary endpoints and speech perception and music perception measures separately for subjects with varying degrees of low frequency hearing loss at 6 months (e.g. 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) hearing loss). This analysis will also be performed based on outcomes at the 3 and 12 month visits. Graphical analysis will be presented examining the primary and secondary endpoints as a function of loss in residual low-frequency hearing and the timing of low-frequency hearing loss. Further, exploratory analyses will be performed to identify factors predictive of low frequency hearing loss, including but not limited to duration of hearing loss, gender, and age. Additional exploratory analyses on hearing loss will incorporate data from G990155 (Hybrid S8) and G070016 (Hybrid S12) studies to provide additional information.

5.8.7 Other Assessments

5.8.7.1 Speech Perception Measures

In a similar fashion to the methods described under sections 4.0 and 5.0, device efficacy will also be assessed for the Combined Mode[24]; that used on an everyday basis by the subjects. Specifically, within-subject differences for the CNC Word Test and AzBio sentences-in-noise test scores taken under the Combined Mode at 6 months postactivation will be compared to those taken under the Bilateral Acoustic condition, pre-operatively. The intention of these analyses is to provide an evaluation of outcomes for subjects using the Hybrid cochlear implant accounting for the fact that the device is used in concert with acoustic hearing in the unimplanted ear.

5.8.7.2 Music Perception Measures

Within-subject differences for the UW-CAMP test scores taken under the Hybrid and Combined Modes at 6 months postactivation will be compared to those taken under the ipsilateral and bilateral acoustic conditions, pre-operatively, respectively. The intention of these analyses is to provide an evaluation of outcomes for subjects using the Hybrid cochlear implant. Results will be compared to outcomes for subjects using traditional cochlear implants (Kang et al., 2009) to demonstrate the usefulness of preserving low-frequency acoustic hearing in Hybrid cochlear implant recipients.

5.8.7.3 Self-Assessment Measures

The Speech, Spatial and Sound Qualities (SSQ) questionnaire, Device Use Questionnaire (DUQ), and Musical Background Questionnaires (MBQ) were administered pre- and

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[24] Scores obtained in the Bimodal Mode will be used in place of Combined Mode for those subjects who did not make use of ipsilateral (i.e., in the implanted ear) acoustic hearing.

post-operatively for the everyday listening mode and scores from this metric will provide secondary measures of device efficacy for the Hybrid cochlear implant when used in the Combined Mode.

Additional exploratory analyses will also involve assessment of the subjects using the Hybrid cochlear implant in the bilateral mode (Combined or Bimodal), reflecting the everyday manner in which the device is used. That is, group and individual outcomes for the subjects using the device in the "everyday" mode (Combined or Bimodal) at 6 months postactivation will be compared to the performance gained in the pre-operative Bilateral Acoustic mode.

5.9 Results and Analysis

5.9.1 Disposition of Subjects

One hundred subjects were consented (50 enrolled/implanted) to be evaluated for participation in the study. Of these 100 subjects:

- 22 failed, not meeting study requirements (listed in Appendix 13, Tab 6):
    - 8 subjects had more than 30 years of severe to profound hearing loss,
    - 4 subjects did not meet speech perception requirements,
    - 4 subjects were unwilling to comply with study requirements (could not commit to study requirements in some manner),
    - 2 subjects did not meet audiometric requirements,
    - 1 subject did not meet speech perception and audiometric requirements,
    - 1 subject had congenital onset of hearing loss,
    - 1 subject had a protocol waiver denied by the site Institutional Review Board (IRB),
    - 1 subject had suspected fluctuating hearing loss.
- 28 were potential candidates (listed in Appendix 13, Tab 6) , but discontinued participation and did not proceed with implantation:

- 16 subjects were not able to secure insurance,
- 8 subjects decided to pursue other options (nonsurgical or traditional cochlear implantation),
  - [redacted] was fit with hearing aids for the first time as part of the candidacy evaluation, decided to continue with amplification rather than pursue cochlear implantation and did not complete Baseline testing.
  - [redacted] was fit with new hearing aids as part of the candidacy evaluation and reportedly and, so pleased with the outcomes, decided to continue with amplification rather than pursue cochlear implantation. The subject didn't feel that the potential benefit outweighed the perceived cosmetic disfigurement of a cochlear implant.
  - [redacted] was reported to not be ready to wear an implant and was not interested in pursuing a surgical procedure.
  - [redacted] consented and completed candidacy testing. Aided word recognition performance was reported to be poorer than unaided performance leading the Sponsor to question the hearing aid fitting that the subject presented with. At that time the site clinician recommended that [redacted] consult with the hearing aid dispenser to potentially improve on the fitting. The subject was undecided on pursuing study participation and did not re-initiate interest in the study at a later time.
  - [redacted] was a Veteran's Affairs recipient who was consented and complete candidacy testing but not prepared to wait for the VA to approve participation in the study. The subject elected to pursue traditional cochlear implantation.

        - [redacted] was consented and completed candidacy testing but upon weighing the potential risks and benefits with the family decided not to pursue implantation due to a concern regarding loss of residual hearing.
        - [redacted] was consented with no preoperative data submitted to the Sponsor for review. The subject's audiologist indicated that [redacted] appeared to be an appropriate candidate for the study but subsequent testing indicated that traditional cochlear implantation was an option that the subject ultimately chose to pursue.
        - [redacted] completed a candidacy evaluation but the site reported that the subject decided to pursue newer hearing aid technology and did not wish to proceed with implantation.
    - 4 subjects did not proceed with surgery when the maximum number of subjects approved for implantation had been met.
- 50 were enrolled and implanted with the Nucleus Hybrid L24 implant.

All 50 implanted subjects had their devices activated and reached the 3-month postactivation test interval. Forty-nine subjects reached the 6-month test interval (endpoint) and 46 subjects completed the 12-month evaluation[25]. The 50 subjects consented but not implanted are listed in Appendix 13, Tab 6 along with their consent date and reason for not proceeding with implantation.

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[25] [redacted] did not complete the 6-month study endpoint after reimplantation with a Nucleus 5 cochlear implant (see case summary for this subject under 5.9.8.2.2.12 Reimplantation after Profound or Total Loss of Low-Frequency Hearing). [redacted] withdrew prior to 12 months after being diagnosed with advancing dementia. [redacted] did not complete the 12 month evaluation following reimplantation with a Nucleus Freedom cochlear implant (see case summary for this subject under 5.9.8.2.2.12 Reimplantation after Profound or Total Loss of Low-Frequency Hearing). [redacted] withdrew prior to reaching the 12-month evaluation after being diagnosed with pancreatic cancer.

5.9.2 Investigational Devices Disposition

During the study, the Sponsor shipped 64 Hybrid cochlear implants to study sites, 50 of which were implanted. The remaining implants provided were backup devices and any not implanted were returned to the Sponsor. Appendix 14, Tab7, lists serial numbers for all 50 Hybrid L24 implants that were implanted under this study, as well as the 14 backup devices returned to the Sponsor.

5.9.3 Protocol Changes and Deviations

5.9.4 Subject Demographics

Demographic data for the 50 subjects implanted with the Nucleus Hybrid L24 are provided in Appendix 15 through 17, Tab 8. The subjects ranged in age at the time of implantation from 23 years to 86.2 years. The duration of hearing loss (of any degree) ranged from 6 years to 84 years. The duration of severe to profound high-frequency hearing loss ranged from 1.6 years to 30.1[26] years. Twenty-five of the subjects were female and 25 were male.

5.9.5 Efficacy Results

At the time of the database closure for this report, speech perception data were available on 50 subjects, for at least one postoperative evaluation. Specifically:

- 50/50 subjects completed the 3-month postactivation interval,

[26] The study limited candidacy to those with no more than 30 years of severe to profound high-frequency hearing loss. Subject [redacted] met this requirement at Candidacy assessment that was completed December 3, 2010, but by the time surgery was completed June 22, 2011 was slightly over 30 years duration.

- 49[27]/50 subjects completed the 6-month postactivation interval, and
- 46[28]/50 subjects completed the 12-month postactivation interval.

The co-primary efficacy endpoints for this study were the assessment of the within-subject difference in CNC word and AzBio sentences-in-noise parameters in the implanted ear at 6 months postactivation (with the device in Hybrid Mode[29]) compared with the preoperative assessment (Acoustic Alone). Secondary efficacy endpoints were that more than 75% of subjects will score equal to or better than the preoperative Acoustic Alone condition on the CNC word measure, CNC phoneme measure, and AzBio sentence-in-noise measure in the Hybrid Mode at 6 months postactivation.

5.9.5.1 Primary Efficacy Endpoint Analyses

The significance of the mean differences between preoperative scores and scores at 6 months postactivation 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), Wilcoxon signed-rank tests were used.

Subject [redacted] did not complete the endpoint evaluation after seeking reimplantation with a Nucleus 5 cochlear implant system. However, this subject did complete the 3-month postactivation evaluation and per the Statistical Analysis Plan (see Appendix 12,

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[27] Subject [redacted] was reimplanted prior to the 6-month interval. Subject [redacted] completed speech perception testing but did not complete an audiometric evaluation; hence the number of subjects at the 6-month evaluation is 49 for efficacy measures and 48 as for the hearing sensitivity data.

[28] Subject [redacted] was reimplanted prior to the 6-month interval. Subject [redacted] was reimplanted prior to the 12-month interval. Subjects [redacted] and [redacted] withdrew prior to the 12-month interval.

[29] Scores obtained in the Cochlear Implant Alone mode were used in place of Hybrid Mode for those subjects who did not make of use of acoustic hearing in the implanted ear.

Tab 5) speech scores from this evaluation were carried forward for primary endpoint analyses only. In addition, sensitivity analyses were performed to assess the robustness of results to different assumptions underlying the missing data. For both the co-primary endpoints, both a best-case and worst-case analysis was performed. The most favorable (best-case) and least favorable (worst-case) change in CNC and AzBio scores observed in the complete data were imputed for the missing values and the data re-analyzed using the full data with the imputed scores. Best case was considered a score of 100% postoperatively (maximum possible) and worst case was considered a score of 0% (minimum possible). Appendices 18 and 19, in Tab 9, provides the individual preoperative and 6-month endpoint data without and with data imputation as outlined above, which is impacted for subject [redacted] only. Statistical analyses output for the various treatments described below can be found in Appendix 20, Tab 10.

5.9.5.1.1.1 Analyses without Imputation

The pre- to postoperative change for the Hybrid Mode at the 6-month postactivation endpoint failed the Shapiro-Wilk test for normality ($p < 0.05$) and was subjected to a Wilcoxon signed-rank test for both the CNC and AzBio measures. As shown in Table 4 below, significant improvement was noted for both test measures. On average, subjects experienced a significant improvement of 36.6 percentage points for CNC word recognition and 32.8 percentage points for AzBio sentences in noise.

Table 4: Statistical summary for co-primary efficacy endpoints, N=49.

(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.

5.9.5.1.1.2 Imputation with a Last Observation Carried Forward (LOCF) Approach

For this analysis, the scores reported for [redacted] at the 3-month evaluation were carried forward for endpoint analysis (Last Observation Carried Forward or LOCF), the rationale being that the subject's withdrawal from the study was related to loss of hearing sensitivity and dissatisfaction with outcomes. The LOCF results are summarized in Table 5 below. Using this approach, the pre- to postoperative gain in speech scores was also significant. On average, subjects experienced a significant improvement of 35.4 percentage points for CNC word recognition and 32.0 percentage points for AzBio sentences in noise.

Table 5: Statistical summary for co-primary efficacy endpoints using the Last Observation Carried Forward (LOCF) approach, N=50.

(N=50)[#]	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%	64.2% ± 26.6%	35.8 ± 27.7 (27.9, 43.7)	p < 0.0001
AzBio scores	16.3% ± 14.4%	48.3% ± 31.3%	32.0 ± 29.4 (23.7, 40.4)	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; last observation was carried forward from the 3-month evaluation.

5.9.5.1.1.3 Imputation using Worst- and Best-Case Approaches

To further confirm the robustness of the endpoint outcomes, the data were also analyzed using Worst-Case and Best-Case approaches. For the former scenario, the 6-month score for subject [redacted] was imputed using a minimum score of 0% (worst possible outcome) and for the latter case a maximum score of 100% was imputed (best possible outcome). The results are summarized in Table 6 below. Using this approach, the pre- to postoperative gains in speech scores were also significant. On average, subjects experienced a significant improvement of 35.3 percentage points for CNC word recognition and 31.9 percentage points for AzBio sentences in noise in the Worst-Case scenario. In the Best-Case situation, subjects experienced a significant improvement of 37.3 percentage points for CNC word recognition and 34.0 percentage points for AzBio sentences in noise.

Table 6: Statistical summary for co-primary efficacy endpoints using Worst-Case, Best-Case approaches, N=50.

(N=50)[#]	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 Worst Case	28.4% ± 14.7%	64.1% ± 26.7%	35.7 ± 27.8 (27.8, 43.6)	p < 0.0001
Word Scores Best Case	28.4% ± 14.7%	66.1% ± 25.6%	37.7 ± 26.8 (30.1, 45.3)	p < 0.0001
AzBio scores Worst Case	16.3% ± 14.4%	48.3% ± 31.3%	32.0 ± 29.4 (23.6, 40.4)	p < 0.0001
AzBio Scores Best Case	16.3% ± 14.4%	50.3% ± 31.4%	34.0 ± 29.9 (25.5, 42.5)	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; Worst-Case and Best-Case scenarios were considered.

These analyses support that both co-primary endpoints were met for this clinical trial, namely:

- The mean score obtained by the subjects using the Hybrid L24 implant system in the Hybrid Mode was significantly improved over that obtained in the Acoustic Alone condition, 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 in the Acoustic Alone condition, preoperatively, for AzBio sentence recognition in noise.

5.9.5.2 Secondary Efficacy Endpoint Analyses

Secondary efficacy endpoint analyses were based on binomial comparisons[30] of pre- and postoperative speech scores for the CNC word recognition test, scored for both word and phoneme correct, and the AzBio sentences-in-noise test. Binomial comparisons of individual scores obtained in the Hybrid Mode 6 months postactivation (key endpoint) were compared with ipsilateral Acoustic Alone (with a hearing aid) scores preoperatively to determine the proportion of subjects performing equal to or better than the preoperative untreated condition. Data imputation methods were not employed for secondary efficacy endpoint analyses.

Appendices 21 through 32 in Tab 11 provide the individual data, which were subject to the secondary analyses, along with binomial comparisons results. As previously stated, secondary efficacy endpoints (based on the performance at the 6-month endpoint in the Hybrid Mode) were as follows:

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

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[30] Thornton, A.R. & Raffin, M.J.M. (1978). Speech discrimination scores modeled as a binomial variable. Journal of Speech and Hearing Research, 21: 507 518.

5.9.5.2.1 Binomial Comparisons

For CNC word recognition in the Hybrid Mode (Appendix 22, Tab 11):

- 48 (96%) of the 49 subjects with speech perception data available performed *equal to or better* postoperatively,
    - 40 (81.6%) of the 49 subjects with speech perception data available performed significantly *better* ($p < .05$) postoperatively, ranging from 14 to 71 percentage points,
    - 8 (16.3%) of the 49 subjects showed no significant pre- to postoperative changes and,
- 1 (2.0%) of the 49 subjects subject showed a significant decrement (-41 percentage points).

For CNC phoneme recognition in the Hybrid Mode (Appendix 26, Tab 11):

- 45 (91.8%) of the 49 subjects with speech perception data available performed *equal to or better* postoperatively,
    - 42 (85.7%) of the 49 subjects with speech perception data available performed significantly *better* ($p < .05$) postoperatively, ranging from 10.3 to 57.7 percentage points,
    - 3 (6.1%) of the 49 subjects showed no significant pre- to postoperative changes and,
- 4 (8.2%) of the 49 subjects subject showed significant decrements (-44.7 to -12.7 percentage points).

For AzBio sentences in noise in the Hybrid Mode (Appendix 30, Tab 11):

- 44 (89.8%) of the 49 subjects with speech perception data available performed *equal to or better* postoperatively,
    - 36 (73.5%) of the 49 subjects with speech perception data available performed significantly *better* ($p < .05$) postoperatively, ranging from 8.1 to 91.5 percentage points,

    - 5 (10.2%) of the 49 subjects showed no significant pre- to postoperative changes and,
- 8 (16.3%) of the 49 subjects subject showed significant decrements (-13.6 to -3.8 percentage points).

Table 7 provides a summary of the binomial comparison outcomes and demonstrates that secondary endpoints for the study were met for all three speech perception metrics. That is, most subjects (> 75%) scored equal to or better than they did in the preoperative ipsilateral Acoustic Alone condition when tested in the Hybrid Mode at the 6-month endpoint.

It is important to consider that in the Combined Mode, normally used by the subjects on a daily basis, 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 in the Bilateral Acoustic condition (i.e., with two hearing aids) 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 is of interest to examine what proportion of the subjects showed significant improvements based on binomial comparisons. Table 8 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 7: Summary of secondary analyses for the Hybrid (endpoint) and 6-Month Combined Modes.

Listening Mode:	Proportion of subjects with postoperative score equal to or better than preoperative score:		
	CNC Words	CNC Phonemes	AzBio in Noise
Hybrid (Study Endpoint)	96.0%	91.8%	89.8%
Combined (Everyday Use)	100%	100%	100%

Table 8: Proportions of subjects scoring significantly better than the preoperative condition (Hybrid Mode vs. Acoustic Alone for the Treated Ear; Combined Mode vs. Bilateral Acoustic for both ears).

Listening Mode:	Proportion of subjects with postoperative score better than preoperative score:		
	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%

5.9.5.3 Effect of Baseline Characteristics on Endpoint Outcomes

The consistency of the primary endpoints was examined across subgroups of subjects defined by the baseline characteristics: gender, age, duration of hearing loss, duration of severe to profound high-frequency hearing loss, etiology, and baseline speech perception scores. Table 9 shows the results of analyses for the CNC word and AzBio sentences-in-noise tests for the treated ear with the relevant statistical outputs provided in Appendix

33, Tab 12. For these analyses, mean benefit for the CNC and AzBio tests in Hybrid Mode were compared segregated based on:

1) Gender (i.e., males vs. females).
2) Median age at implantation (i.e., < 68 years or ≥ 68 years).
3) Median duration of hearing loss (i.e., < 23.5 years or ≥ 23.5 years).
4) Median duration of severe to profound high-frequency hearing loss (i.e., < 21.7 years or ≥ 11.7 years).
5) Etiology of hearing loss.
6) Median preoperative baseline scores for CNC (< 24% years or ≥ 24%) and AzBio(< 14.2% years or ≥ 14.2%) in the ipsilateral, Acoustic Alone condition.

Results indicated that the baseline characteristics of gender, age, and duration of hearing loss were the main factors in terms of speech perception outcomes. This was not the case for duration of severe to profound high-frequency hearing loss, etiology of hearing loss, and baseline speech scores. Mean benefit scores (i.e., improvement) for females were significantly greater than males for the CNC words and AzBio tests ($p = 0.002$ and 0.02, respectively), as shown in Appendix 33, Tab 12. Subjects under the median age at implantation of 68 years-of-age, showed significantly greater benefit for the CNC test ($p = 0.012$) but not AzBio sentences in noise ($p = 0.052$); though the trend was in favor of the younger subjects. The mean benefit score for subjects above the median duration of hearing loss of 23.5 years was significantly better ($p = 0.012$) than that for durations of hearing loss below 23.5 years for the CNC but not AzBio sentences in noise ($p = 0.054$); though the trend was in favor of shorter durations of hearing loss.

Table 9: Subgroup analyses of baseline characteristics effects on 6-Month endpoint outcomes.

Outcome Measure	Gender P-value*	Age P-value*	Duration of Loss P-value*	Duration of Severe to Profound HF Loss P-value*	Etiology P-value*	Baseline CNC Score P-value*	Baseline AzBio Score P-value*
CNC Words	0.002	0.012	0.012	0.619	0.313	.164	.518
AzBio in Noise	0.02	0.052	0.054	0.886	0.596	.94	.947

*ANOVA p-value.

5.9.5.3.1 Site Effects

Similarly, 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 was associated with a p-value less than 0.10 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 Acoustic Alone scores) observed for both the CNC ($p = 0.42$) and AzBio ($p = 0.63$) tests in the treated ear condition (Appendix 33, Tab 12). Figure 2 shows the mean pre- and 6-month postactivation scores for each site for the CNC (top) and AzBio tests (bottom). Although absolute scores vary somewhat site to site all sites demonstrate significant improvement in mean scores. Figure 3 plots similar data for the normal, bilateral use mode (Combined Mode) for reference.

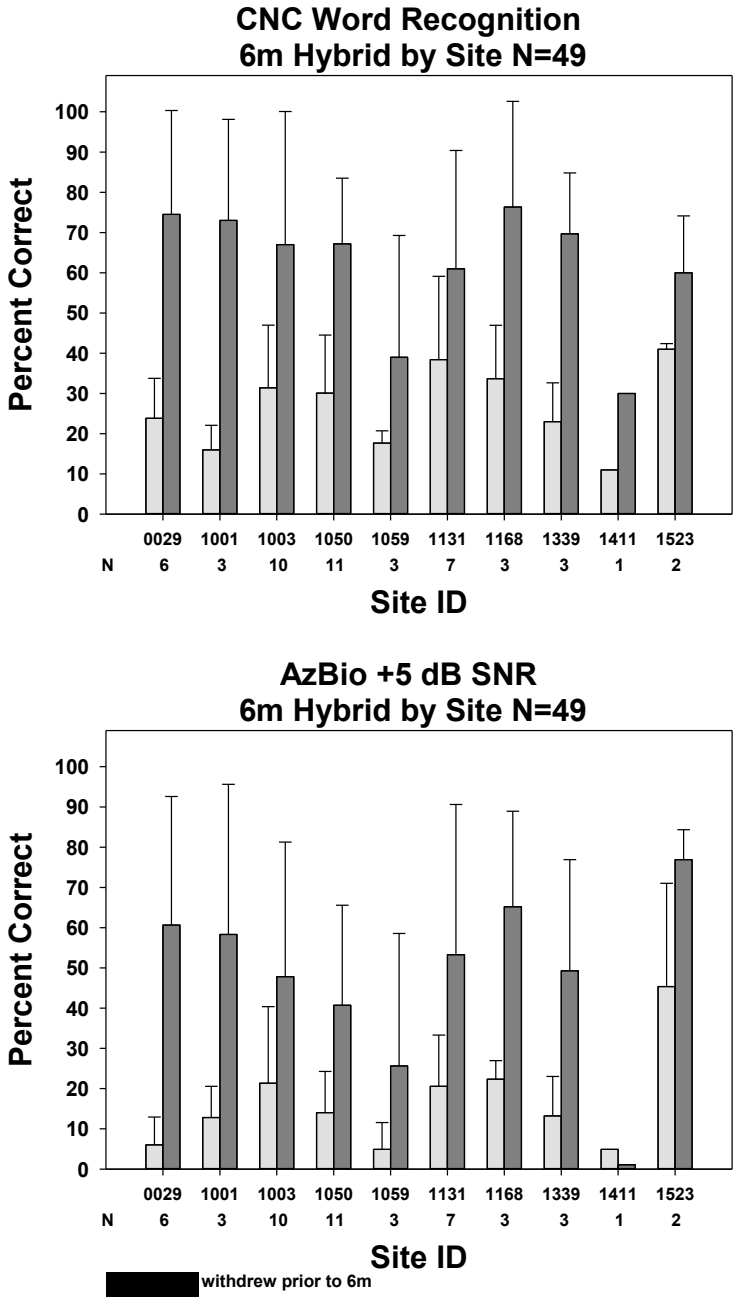

Figure 2: Mean pre- and postoperative CNC (top) and AzBio sentences-in-noise (bottom) scores for each study site for the Hybrid Mode. Subject [redacted] was reimplanted prior to 6 months postactivation.

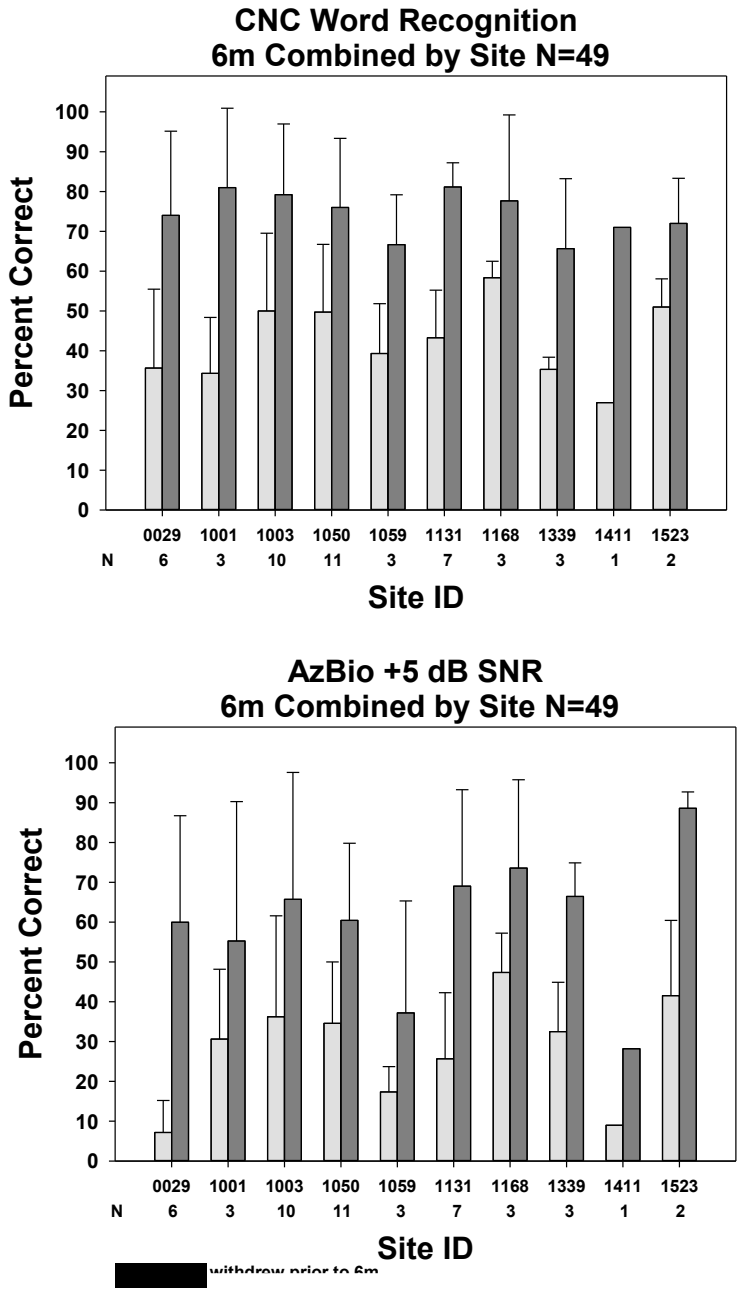

Figure 3: Mean pre- and postoperative CNC (top) and AzBio sentences-in-noise (bottom) scores for each study site for the Combined Mode. Subject [redacted] was reimplanted prior to 6 months postactivation.

5.9.5.4 Efficacy Analyses Overtime

What follows is a summary of the group efficacy outcomes over the 12-month study period during which speech perception measures were made. Group summary and individual speech perception data can be found in Tab 11 for the two primary efficacy measures: CNC words (Appendices 21, 23, 25, and 27) and AzBio sentences in noise (Appendices 29, and 31). The results from statistical analyses are detailed in Tab 10.

5.9.5.4.1 CNC Word Recognition

5.9.5.4.1.1 Ipsilateral Condition

For the 50 subjects with pre- and postoperative data (Appendix 21, Tab 11):

- Preoperative CNC word scores obtained Acoustic Alone (with a hearing aid in the ipsilateral, ear to be implanted) ranged from 9% to 64%, with a mean score of 28.4% (N=50),
- At the 3 month postactivation test interval, performance in the Hybrid Mode (i.e., Cochlear Implant + Ipsilateral Acoustic[31]) ranged from 3% to 93%, with a mean of 58.5% (N=50),
- At the 6-month endpoint, scores ranged from 8% to 98% with a mean of 65.4% (N=49), and
- At 12 months, scores ranged from 5% to 97% with a mean of 69.4% (N=46).

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[31] Note that for subjects [redacted], and [redacted] the Hybrid Mode was not tested at 3 months because the subjects experienced profound or total loss of hearing and did not derive benefit from the Acoustic Component of the Hybrid device. Thus, preoperative Acoustic Alone scores were compared with the postoperative Hybrid cochlear implant alone condition. This was the case at 6 months for [redacted]. This was the case at 12 months for [redacted]

All pre-to-postoperative mean differences were significant (including the pre- to 6-month endpoint comparison) based on paired t-tests[32] as summarized in Table 10 below.

By 12 months postactivation, binomial comparisons of the Hybrid Mode and Acoustic Alone scores preoperatively (Appendix 22, Tab 11), showed that 40 (87.0%) of the 46 subjects with speech perception data available performed significantly better ($p < .05$) postoperatively. Five subjects showed significant decrements and 1 subject showed no significant pre- to postoperative change.

Table 10: Pre- to postoperative statistical outcomes for the CNC word recognition test in the Hybrid Mode.

Pre-to-Post Comparison	Percentage Point Change Mean ± S.D. (95% C.I)	t (Paired t-test) or S (Signed-Rank Test)	P-Value*
3 Months Postactivation	30.1 ± 26.5 (22.5, 37.6)	t(49) = 8.01	P < 0.0001
6 Months Postactivation	37.0 ± 26.6 (29.4, 44.6)	t(48) = 9.74	P < 0.0001
12 Months Postactivation	40.3 ± 29.1 (31.7, 49.0)	S = 499.5	P < 0.0001

*Student's t-test p-value; signed-rank p-value if normality assumption failed.

[32] If there was significant evidence that the assumptions of the t-test were not met (i.e., $p < 0.05$ for a Shapiro-Wilk test of normality), a Wilcoxon signed-rank test was used instead.

5.9.5.4.1.2 Bilateral Condition

For the 50 subjects with pre- and postoperative data (Appendix 23, Tab 11):

- Preoperative CNC word scores obtained in the Bilateral Acoustic mode (with bilateral hearing aids) ranged from 2% to 81%, with a mean score of 44.9% (N=50),
- At the 3 month postactivation test interval, performance in the Combined Mode (i.e., Cochlear Implant + Bilateral Acoustic[33]) ranged from 27% to 98%, with a mean of 75.9% (N=50),
- At 6 months scores ranged from 35% to 98% with a mean of 79.4% (N=49), and
- At 12 months scores ranged from 44% to 98% with a mean of 82.0% (N=46).

All pre-to-postoperative mean differences were significant (including the pre- to 6-month endpoint comparison) based on paired t-tests as summarized in Table 11 below.

By 12 months postactivation, binomial comparisons of the Combined Mode and Bilateral Acoustic scores preoperatively (Appendix 24, Tab 11), showed that 40 (87.0%) of the 46 subjects with speech perception data available performed significantly better ($p < .05$) postoperatively. Six subjects showed no significant pre- to postoperative changes. No subject showed a significant decrement.

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[33] Note that for subjects [redacted] and [redacted] the Combined Mode was not tested at 3 months because the subjects experienced profound or total loss of hearing and did not derive benefit from the Acoustic Component of the Hybrid device. Thus, preoperative Bilateral Acoustic scores were compared with the postoperative Bimodal Mode condition. This was the case at 6 months for [redacted], and [redacted] This was the case at 12 months for [redacted], and [redacted].

Table 11: Pre- to postoperative statistical outcomes for the CNC word recognition test in the Combined Mode.

Pre-to-Post Comparison	Percentage Point Change Mean ± S.D. (95% C.I)	t (Paired t-test) or S (Signed-Rank Test)	P-Value*
3 Months Postactivation	31.0 ± 18.4 (25.8, 36.3)	t(49) = 11.9	P < 0.0001
6 Months Postactivation	34.7 ± 17.4 (29.7, 39.7)	t(48) = 13.94	P < 0.0001
12 Months Postactivation	36.8 ± 19.1 (31.1, 42.4)	t(45) = 13.07	P < 0.0001

*Student's t-test p-value; signed-rank p-value if normality assumption failed.

5.9.5.5 CNC Phoneme Recognition

5.9.5.5.1 Ipsilateral Condition

For the 50 subjects with pre- and postoperative data (Appendix 25, Tab 11):

- Preoperative CNC word scores obtained Acoustic Alone (with a hearing aid in the ipsilateral, ear to be implanted) ranged from 25.7% to 81.7%, with a mean score of 51.4% (N=50),

- At the 3 month postactivation test interval, performance in the Hybrid Mode (i.e., Cochlear Implant + Ipsilateral Acoustic[34]) ranged from 9% to 97%, with a mean of 73.0% (N=50),
- At 6 months scores ranged from 26.3% to 99.3% with a mean of 78.3% (N=49), and
- At 12 months scores ranged from 25.7% to 98.7% with a mean of 81.5% (N=46).

All pre-to-postoperative mean differences were significant (including the pre- to 6-month endpoint comparison) based on paired t-tests as summarized in Table 12 below.

By 12 months postactivation, binomial comparisons of the Hybrid Mode and Acoustic Alone scores preoperatively (Appendix 26, Tab 11), showed that 40 (87.0%) of the 46 subjects with speech perception data available performed significantly better ($p < .05$) postoperatively. Five subjects showed significant decrements pre- to postoperative changes. One subject showed no significant change.

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[34] Note that for subjects [redacted] the Hybrid Mode was not tested at 3 months because the subjects experienced profound or total loss of hearing and did not derive benefit from the Acoustic Component of the Hybrid device. Thus, preoperative Acoustic Alone scores were compared with the postoperative Hybrid cochlear implant alone condition. This was the case at 6 months for [redacted]. This was the case at 12 months for [redacted].

Table 12: Pre- to postoperative statistical outcomes for the CNC phoneme recognition test in the Hybrid Mode.

Pre-to-Post Comparison	Percentage Point Change Mean ± S.D. (95% C.I)	t (Paired t-test) or S (Signed-Rank Test)	P-Value*
3 Months Postactivation	21.6 ± 23.5 (14.9, 28.3)	S = 503	P < 0.0001
6 Months Postactivation	27.0 ± 23.0 (20.4, 33.6)	S = 529.5	P < 0.0001
12 Months Postactivation	29.4 ± 23.9 (22.3, 36.5)	S = 480.5	P < 0.0001

*Student's t-test p-value; signed-rank p-value if normality assumption failed.

5.9.5.5.2 Bilateral Condition

For the 50 subjects with pre- and postoperative data (Appendix 27, Tab 11):

- Preoperative CNC phoneme scores obtained in the Bilateral Acoustic mode (with bilateral hearing aids) ranged from 19.7% to 92.7%, with a mean score of 67.6% (N=50),
- At the 3 month postactivation test interval, performance in the Combined Mode (i.e., Cochlear Implant + Bilateral Acoustic[35]) ranged from 57.3% to 99.3%, with a mean of 87.7% (N=50),

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[35] Note that for subjects [redacted] the Combined Mode was not tested at 3 months because the subjects experienced profound or total loss of hearing and did not derive benefit from the Acoustic Component of the Hybrid device. Thus, preoperative Bilateral Acoustic scores were compared with the postoperative

- At 6 months scores ranged from 55% to 99.3% with a mean of 89.8% (N=49), and
- At 12 months scores ranged from 61% to 99.3% with a mean of 91.1% (N=46).

All pre-to-postoperative mean differences were significant (including the pre- to 6-month endpoint comparison) based on paired t-tests as summarized in Table 13 below.

By 12 months postactivation, binomial comparisons of the Combined Mode and Bilateral Acoustic scores preoperatively (Appendix 28, Tab 11), showed that 41 (89.1%) of the 46 subjects with speech perception data available performed significantly better ($p < .05$) postoperatively. Five subjects showed no significant pre- to postoperative changes. No subject showed a significant decrement.

Bimodal Mode condition. This was the case at 6 months for [redacted] This was the case at 12 months for [redacted]

Table 13: Pre- to postoperative statistical outcomes for the CNC phoneme recognition test in the Combined Mode.

Pre-to-Post Comparison	Percentage Point Change Mean ± S.D. (95% C.I)	t (Paired t-test) or S (Signed-Rank Test)	P-Value*
3 Months Postactivation	20.1 ± 13.5 (16.3, 24.0)	S = 633.5	P < 0.0001
6 Months Postactivation	22.3 ± 13.3 (18.5, 26.2)	t(48) = 11.76	P < 0.0001
12 Months Postactivation	23.4 ± 14.1 (19.2, 27.6)	t(45) = 11.26	P < 0.0001

*Student's t-test p-value; signed-rank p-value if normality assumption failed.

5.9.5.6 AzBio Sentences in Noise

5.9.5.6.1 Ipsilateral Condition

For the 50 subjects with pre- and postoperative data (Appendix 29, Tab 11):

- Preoperative AzBio sentence scores obtained with a hearing aid in the ipsilateral ear (i.e., the ear to be implanted) ranged from 0% to 64.1%, with a mean score of 16.3% (N=50),

- At the 3 month postactivation test interval, performance in the Hybrid Mode (i.e., Cochlear Implant + Ipsilateral Acoustic[36]) ranged from 0% to 88.7%, with a mean of 44.6% (N=49),
- At 6 months scores ranged from 0% to 91.5% with a mean of 49.2% (N=49), and
- At 12 months scores ranged from 0% to 90.2% with a mean of 51.5% (N=46).

All pre-to-postoperative mean differences were significant (including the pre- to 6-month endpoint comparison) based on paired t-tests as summarized in Table 14 below. By 12 months postactivation, binomial comparisons of the Hybrid Mode and Acoustic Alone scores preoperatively (Appendix 30, Tab 11), showed that 33 (71.7%) of the 46 subjects with speech perception data available performed significantly better ($p < .05$) postoperatively. Five subjects showed significant decrements and 8 subjects showed no significant pre- to postoperative changes.

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[36] Note that for subjects [redacted] and [redacted] the Hybrid Mode was not tested at 3 months as the best unilateral listening mode usually because the subjects experienced profound or total loss of hearing and did not derive benefit from the Acoustic Component of the Hybrid device. Thus, preoperative Acoustic Alone scores were compared with the postoperative Hybrid cochlear implant alone as the best unilateral listening condition. This was the case at 6 months for [redacted] and [redacted] This was the case at 12 months for [redacted]

Table 14: Pre- to Postoperative Statistical Outcomes for the AzBio Test at +5 dB SNR in the Hybrid Mode.

Pre-to-Post Comparison	Percentage Point Change Mean ± S.D. (95% C.I)	t (Paired t-test) or S (Signed-Rank Test)	P-Value*
3 Months Postactivation	28.1 ± 30.5 (19.4, 36.9)	t(49) = 6.47	P < 0.0001
6 Months Postactivation	32.8 ± 29.1 (24.5, 41.2)	S = 506	P < 0.0001
12 Months Postactivation	34.2 ± 29.5 (25.5, 43.0)	t(45) = 7.87	P < 0.0001

*Student's t-test p-value; signed-rank p-value if normality assumption failed.

5.9.5.6.2 Bilateral Condition

For the 50[37] subjects with pre- and postoperative data (Appendix 31, Tab 11):

- Preoperative AzBio sentence scores obtained with bilateral hearing aids ranged from 0% to 76.5%, with a mean score of 29.6% (N=50),
- At the 3 month postactivation test interval, performance in the Combined Mode (i.e., Cochlear Implant + Bilateral Acoustic[38]) ranged from 0% to 97.3%, with a mean of 62.6% (N=49[39]),

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[37] The 3-month score for [redacted] was identified as a possible outlier. The subject's score was recorded as 80.3% and not consistent with overall performance. However, analyses with and without this subject's score did not differ in that mean pre- to postoperative improvement was not significantly different. In addition, the inclusion of the score at 3 months did not impact endpoint outcomes.

[38] Note that for subjects [redacted] the Combined Mode

- At 6 months scores ranged from 3.6% to 92.7% with a mean of 62.6% (N=49), and
- At 12 months scores ranged from 3.6% to 97.5% with a mean of 66.3% (N=46).

All pre-to-postoperative mean differences were significant (including the pre- to 6-month endpoint comparison) based on paired t-tests as summarized in Table 15 below.

By 12 months postactivation, binomial comparisons of the Combined Mode and Bilateral Acoustic scores preoperatively (Appendix 32, Tab 11), showed that 41 (89.1%) of the 46 subjects with speech perception data available performed significantly better ($p < .05$) postoperatively. Three subjects showed no significant pre- to postoperative changes. Two subjects showed significant decrements.

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was not tested as the best bilateral listening mode at 3 months usually because the subjects experienced profound or total loss of hearing and did not derive benefit from the Acoustic Component of the Hybrid device. Thus, preoperative Bilateral Acoustic scores were compared with the postoperative Bimodal Mode as the best bilateral listening mode. This was the case at 6 months for [redacted] This was the case at 12 months for [redacted]

[39] [redacted] not tested on the AzBio test at 3 months.

Table 15: Pre- to postoperative statistical outcomes for the AzBio test at +5 dB SNR in the Combined Mode.

Pre-to-Post Comparison	Percentage Point Change Mean ± S.D. (95% C.I.)	t (Paired t-test) or S (Signed-Rank Test)	P-Value*
3 Months Postactivation	33.1 ± 24.6 (26.0, 40.2)	t(48) = 9.41	P < 0.0001
6 Months Postactivation	33.0 ± 23.5 (26.2, 39.7)	t(48) = 9.80	P < 0.0001
12 Months Postactivation	35.8 ± 24.6 (28.5, 43.1)	t(45) = 9.87	P < 0.0001

*Student's t-test p-value; signed-rank p-value if normality assumption failed.

5.9.5.7 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 each designed to provide an assessment of fundamental auditory skills important for music perception. One subtest provided an assessment of pitch discrimination, the second provided an assessment of melody recognition and the third subtest assessed the perception of timbre. The UW-CAMP was administered ipsilaterally for the implanted ear and bilaterally at the preoperative baseline and 6-month endpoint evaluations.

It is generally accepted that traditional cochlear implantation delivers the potential for significantly improved speech perception but music perception/appreciation remains relatively poor via electrical stimulation (Kang et al., 2009). Results were compared with outcomes for subjects using traditional cochlear implants (from Kang et al., 2009) to

demonstrate the usefulness of maintaining low-frequency acoustic hearing in Hybrid cochlear implant recipients.

5.9.5.7.1 Pitch Discrimination Subtest

5.9.5.7.1.1 Ipsilateral Condition

Tab 13 provides the raw data for the Pitch Discrimination subtest of the UW-CAMP. Pitch discrimination was assessed for three base frequencies, 262, 330, and 392 Hz. Pitch discrimination thresholds obtained for the base frequencies were also averaged to derive a single pitch score and described below, though scores for all 3 base frequencies can be seen in Appendix 34, Tab 13.

For the 50 subjects with pre- and postoperative data:

- Average preoperative pitch discrimination thresholds obtained Acoustic Alone, with a hearing aid in the ipsilateral ear (i.e., the ear to be implanted), ranged from 0.5 to 4.8 semitones, with a mean of 1.1 semitones (N=50),
- At the 6 month postactivation test interval, performance in the Hybrid Mode (i.e., Cochlear Implant + Ipsilateral Acoustic[40]) ranged from 0.5 to 8.9 semitones, with a mean of 1.5 semitones (N=46[41]).

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[40] Note that for subjects [redacted] the Hybrid Mode was not tested at 6 months as the best unilateral listening mode because the subjects experienced profound or total loss of hearing and did not derive benefit from the Acoustic Component of the Hybrid device. Thus, preoperative Acoustic Alone scores were compared with the postoperative Hybrid cochlear implant alone as the best unilateral listening condition.

[41] The score for [redacted] did not save due to a software error, [redacted] was not assessed as this subject did not understand the task (and was subsequently diagnosed with advancing dementia), [redacted] did not complete the test due to time constraints, and [redacted] was reimplanted prior to the 6-month interval.

5.9.5.7.1.2 Bilateral Condition

Appendix 35, Tab 13 provides the raw data for the Pitch Discrimination subtest of the UW-CAMP for Bilateral Acoustic, preoperatively, and Combined Mode at the 6-month postactivation interval.

For the 50 subjects with pre- and postoperative data:

- Average preoperative pitch discrimination thresholds obtained in the Bilateral Acoustic condition, with bilateral hearing aids, ranged from 0.5 to 6.3 semitones, with a mean of 1.1 semitones (N=50),
- At the 6 month postactivation test interval, performance in the Combine Mode (i.e., Cochlear Implant + Bilateral Acoustic[42]) ranged from 0.5 to 3.7 semitones, with a mean of 1.1 semitones (N=46[43]).

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[42] Note that for subjects [redacted] 339 the Combined Mode was not tested at 6 months as the best bilateral listening mode because the subjects experienced profound or total loss of hearing and did not derive benefit from the Acoustic Component of the Hybrid device. Thus, preoperative Bilateral Acoustic scores were compared with the postoperative Bimodal Mode as the best bilateral listening condition.

[43] The score for [redacted] did not save due to a software error, [redacted] was not assessed as this subject did not understand the task (and was subsequently diagnosed with advancing dementia), [redacted] did not complete the test due to time constraints, and [redacted] was reimplanted prior to the 6-month interval.

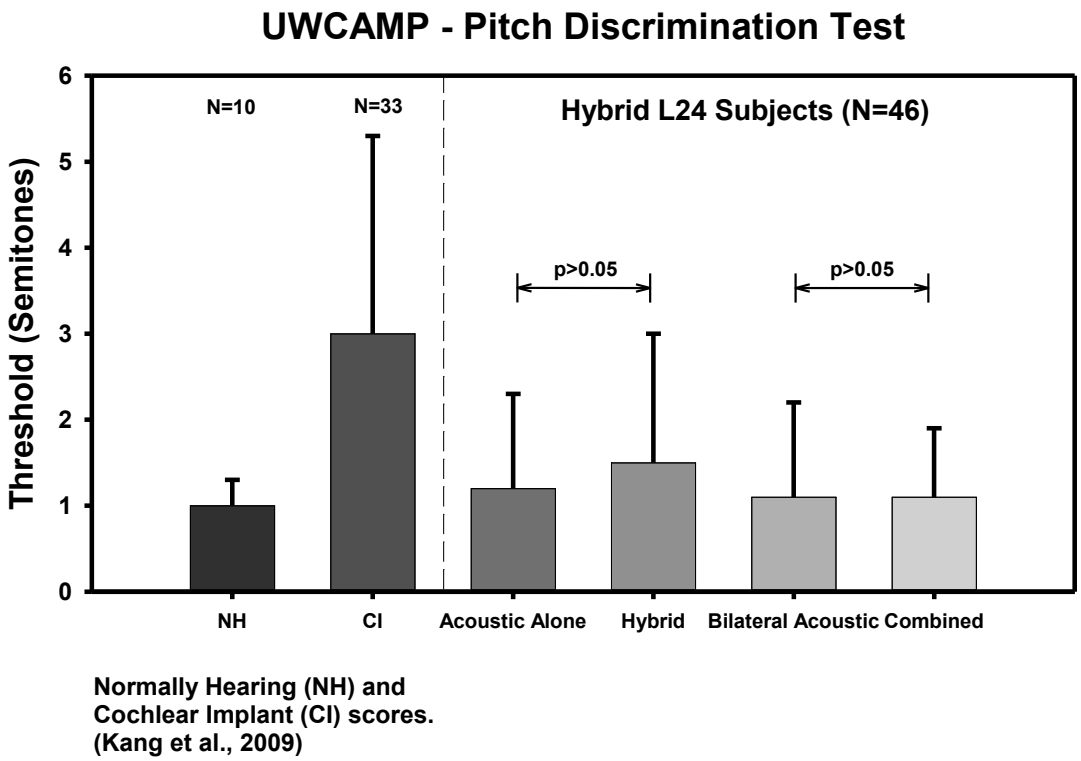

Figure 4: UW-CAMP mean pitch discrimination thresholds for normally hearing and traditional cochlear implant users (left) and Hybrid recipients (right).

Mean scores for the Hybrid subjects are contrasted with normally hearing individuals and traditional cochlear implant users from Kang et al. (2009) in Figure 4. As shown, normally hearing individuals can discriminate tones that are 1 semitone apart on average, whereas traditional cochlear implant recipients require the tones to be 3 semitones apart, on average. Hybrid users (to the right) perform at a levels similar to that observed for the normally hearing subjects from Kang et al. and considerably better than that observed for the traditional cochlear implant users from that same study. In addition, the Hybrid users maintained their pitch discrimination abilities, on average pre- to postoperatively for the treated ear (Acoustic Alone vs. Hybrid Mode) and when considering scores for the bilateral condition (Bilateral Acoustic vs. Combined Mode). No significant changes ($p > 0.05$) were noted when comparing Acoustic Alone (preoperatively) and Hybrid Mode

(two middle bars) as well as Bilateral Acoustic (preoperatively) and Combined Mode (two bars to the right). Statistical outputs can be viewed in Appendix 36, Tab 13.

5.9.5.7.2 Melody Recognition Subtest

5.9.5.7.2.1 Ipsilateral Condition

Melody recognition was assessed by asking subjects to identify a familiar melody from a closed-set of 12 possible alternatives (i.e., the chance of a correct response was 1/12 or 8.3%). Percent scores obtained for the subjects, pre- and postoperatively, can be seen in Appendix 37, Tab 14.

For the 50 subjects with pre- and postoperative data:

- Preoperative melody recognition scores obtained Acoustic Alone ranged from 11.1% to 100%, with a mean of 66.2% (N=50),
- At the 6 month postactivation test interval, performance in the Hybrid Mode[44] also ranged from 11.1% to 100%, with a mean of 65.9% (N=47[45]).

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[44] Note that for subject [redacted] and [redacted] the Hybrid Mode was not tested at 6 months as the best unilateral listening mode because the subjects experienced profound or total loss of hearing and did not derive benefit from the Acoustic Component of the Hybrid device. Thus, preoperative Acoustic Alone scores were compared with the postoperative Hybrid cochlear implant alone as the best unilateral listening condition.

[45] [redacted] was not assessed as this subject did not understand the task (and was subsequently diagnosed with advancing dementia), [redacted] not complete the test due to time constraints, and [redacted] was reimplanted prior to the 6-month interval.

5.9.5.7.2.2 Bilateral Condition

Appendix 37, Tab 14 provides the raw data for the Melody Recognition subtest of the UW-CAMP.

For the 50 subjects with pre- and postoperative data:

- Preoperative melody recognition scores obtained in the Bilateral Acoustic condition ranged 13.9% to 100%, with a mean of 66.3% (N=50),
- At the 6 month postactivation test interval, performance in the Combined Mode[46] ranged from 16.7% to 100%, with a mean of 66.7% (N=46[47]).

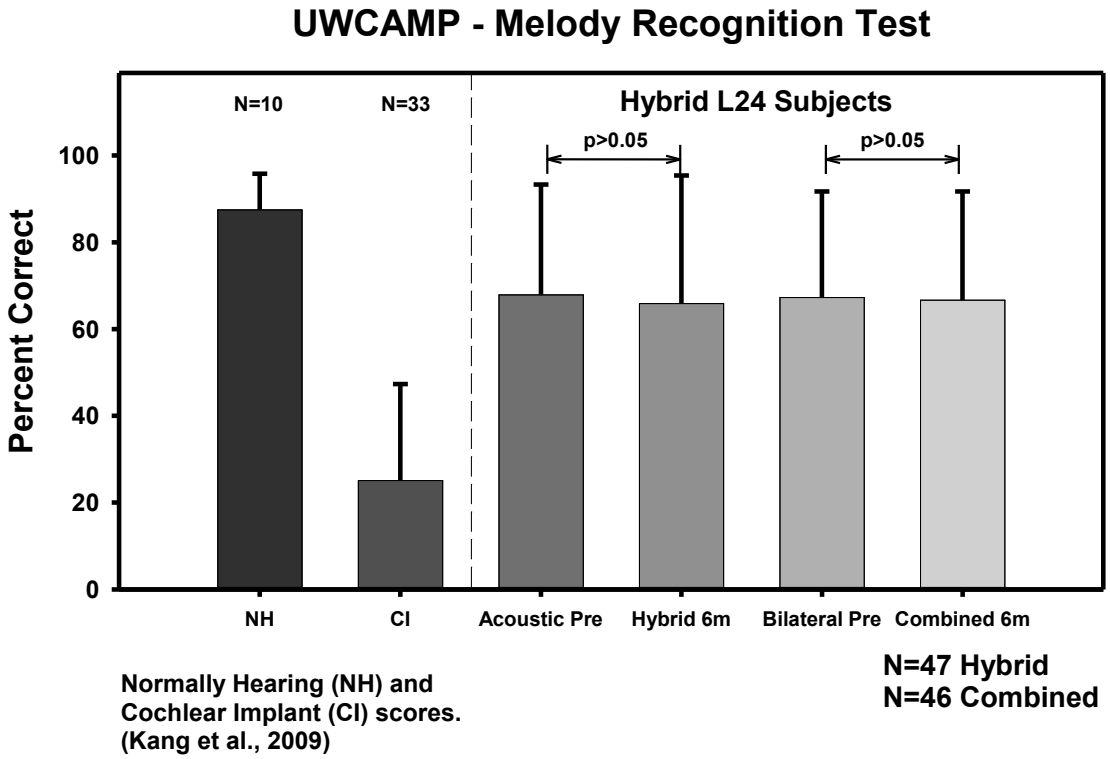

Figure 5: UW-CAMP mean melody recognition scores for normally hearing and traditional cochlear implant users (left) and Hybrid recipients (right).

[46] Note that for subjects [redacted] the Combined Mode was not tested at 6 months as the best bilateral listening mode because the subjects experienced profound or total loss of hearing and did not derive benefit from the Acoustic Component of the Hybrid device. Thus, preoperative

Mean scores for the Hybrid subjects are contrasted with normally hearing individuals and traditional cochlear implant users from Kang et al. (2009) in Figure 5. As shown, normally hearing individuals correctly recognized familiar melodies with a mean score of 87.5%, whereas traditional cochlear implant recipients scored 25.1% correct, on average. Hybrid users (to the right) perform at a level somewhat poorer than that observed for the normally hearing subjects but considerably better than that observed for traditional cochlear implant users. Importantly, the Hybrid users maintained their melody recognition abilities, on average pre- to postoperatively for the treated ear (Acoustic Alone vs. Hybrid Mode) and for the bilateral condition (Bilateral Acoustic vs. Combined Mode). No significant changes ($p > 0.05$) were noted when comparing Acoustic Alone (preoperatively) and Hybrid Mode (two middle bars) as well as Bilateral Acoustic (preoperatively) and Combined Mode (two bars to the right). Statistical outputs can be viewed in Appendix 36, Tab 13.

5.9.5.7.3 Timbre Recognition Subtest

5.9.5.7.3.1 Ipsilateral Condition

Timbre recognition was assessed by asking subjects to identify an instrument type from a closed-set of 8 possible alternatives (i.e., the chance of a correct response was 1/8 or 12.5%). Percent scores obtained for the subjects, pre- and postoperatively, can be seen in Appendix 37, Tab 14.

Bilateral Acoustic scores were compared with the postoperative Bimodal Mode as the best bilateral listening condition.

[47] The score for [redacted] did not save due to a software error, [redacted] was not assessed as this subject did not understand the task (and was subsequently diagnosed with advancing dementia), [redacted] did not complete the test due to time constraints, and [redacted] was reimplanted prior to the 6-month interval.

For the 50 subjects with pre- and postoperative data:

- Preoperative timbre recognition scores obtained Acoustic Alone ranged from 12.5% to 91.7%, with a mean of 50.8% (N=50),
- At the 6 month postactivation test interval, performance in the Hybrid Mode[48] ranged from 8.3% to 100%, with a mean of 56.6% (N=47[49]).

5.9.5.7.3.2 Bilateral Condition

Appendix 37, Tab 14 provides the raw data for the Timbre Recognition subtest of the UW-CAMP.

For the 50 subjects with pre- and postoperative data:

- Preoperative timbre recognition scores obtained in the Bilateral Acoustic condition ranged 8.3% to 100%, with a mean of 56.2% (N=50),
- At the 6 month postactivation test interval, performance in the Combined Mode[50] ranged from 20.8% to 91.7%, with a mean of 57.0% (N=46[51]).

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[48] Note that for subjects [redacted] the Hybrid Mode was not tested at 6 months as the best unilateral listening mode because the subjects experienced profound or total loss of hearing and did not derive benefit from the Acoustic Component of the Hybrid device. Thus, preoperative Acoustic Alone scores were compared with the postoperative Hybrid cochlear implant alone as the best unilateral listening condition.

[49] [redacted] was not assessed as this subject did not understand the task (and was subsequently diagnosed with advancing dementia), [redacted] did not complete the test due to time constraints, and [redacted] was reimplanted prior to the 6-month interval.

[50] Note that for subjects [redacted] the Combined Mode was not tested at 6 months as the best bilateral listening mode because the subjects experienced profound or total loss of hearing and did not derive benefit from the Acoustic Component of the Hybrid device. Thus, preoperative Bilateral Acoustic scores were compared with the postoperative Bimodal Mode as the best bilateral listening condition.

[51] The score for [redacted] did not save due to a software error, [redacted] was not assessed as this subject did not understand the task (and was subsequently diagnosed with advancing dementia), [redacted]

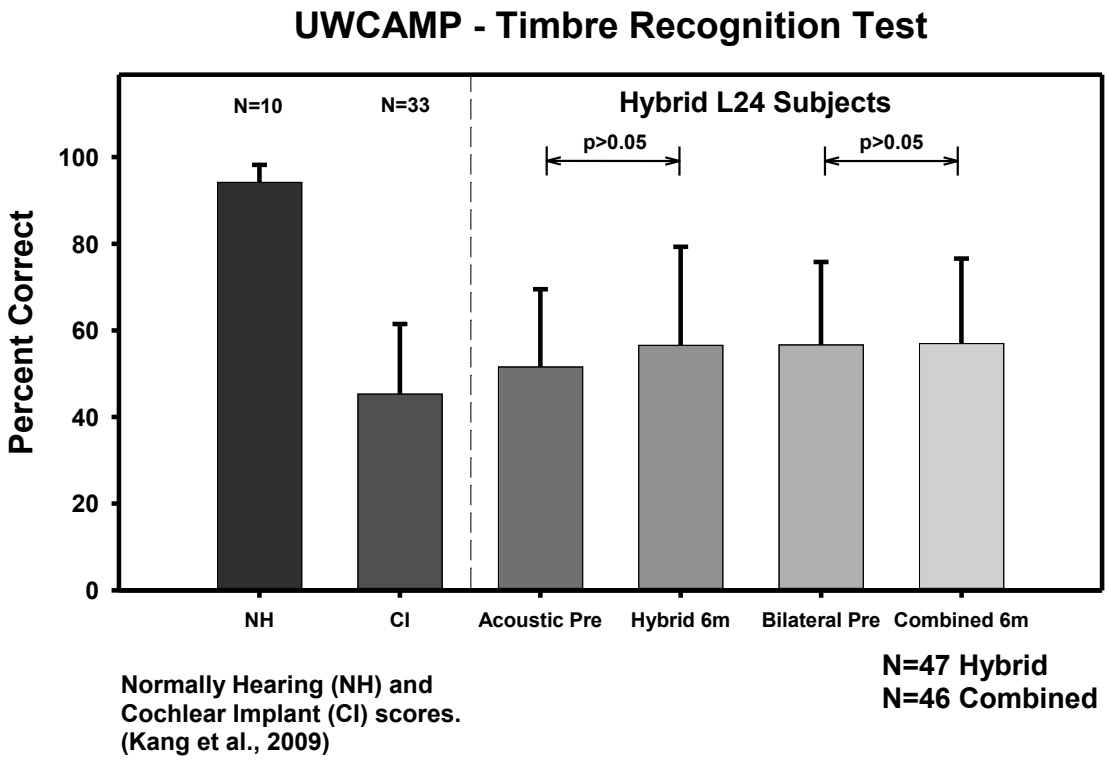

Figure 6: UW-CAMP mean timbre recognition scores for normally hearing and traditional cochlear implant users (left) and Hybrid recipients (right).

Mean scores for the Hybrid subjects are contrasted with normally hearing individuals and traditional cochlear implant users from Kang et al. (2009) in Figure 6. As shown, normally hearing individuals correctly recognized familiar melodies with a mean score of 87.5%, whereas traditional cochlear implant recipients scored 25.1% correct, on average. Hybrid users (to the right) perform at a level somewhat poorer than that observed for the normally hearing subjects but considerably better than that observed for traditional cochlear implant users. Importantly, the Hybrid users maintained their melody recognition abilities, on average pre- to postoperatively for the treated ear (Acoustic

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[redacted] did not complete the test due to time constraints, and [redacted] was reimplanted prior to the 6-month interval.

Alone vs. Hybrid Mode) and for the bilateral condition (Bilateral Acoustic vs. Combined Mode). No significant changes ($p > 0.05$) were noted when comparing Acoustic Alone (preoperatively) and Hybrid Mode (two middle bars) as well as Bilateral Acoustic (preoperatively) and Combined Mode (two bars to the right). Statistical outputs can be viewed in Appendix 36, Tab 13.

5.9.5.8 Speech Reception Threshold (SRT) Test

Speech Reception Threshold (SRT) for spondees in the presence of competing talkers was measured as an assessment of speech perception in spatially separated noise. Of specific interest was quantifying the potential advantage to be derived by maintaining useful low-frequency acoustic hearing ipsilateral to the implant in addition to the contralateral ear. SRT was measured with the target signal located in front of the listener (0° azimuth) and the competing signal directed towards the implanted ear (at 90° azimuth) or towards the contralateral ear in the following acoustic listening modes preoperatively:

- Contralateral Acoustic alone and,
- Bilateral Acoustic.

Postoperatively at 6 months postactivation, the following conditions were assessed:

- Bimodal mode and,
- Combined Mode.

The primary interest was whether or not the addition of ipsilateral acoustic hearing in the Combined Mode provided additional benefit, associated with spatial separation of the target speech and noise, over that offered by the Bimodal Mode when acoustic information was delivered primarily from the contralateral ear only. In particular, it was of interest if this advantage existed for the condition where the competing noise was directed towards the implanted ear as this would imply that the listener is able to take advantage of cues related to release from masking. To that end, SRTs measured when

noise was directed towards the implanted ear are plotted in Figure 7, although Appendices 38 and 39, Tab 15 contains the data obtained for the condition where the competing noise was directed toward the contralateral ear, in addition to the ipsilateral ear, for reference.

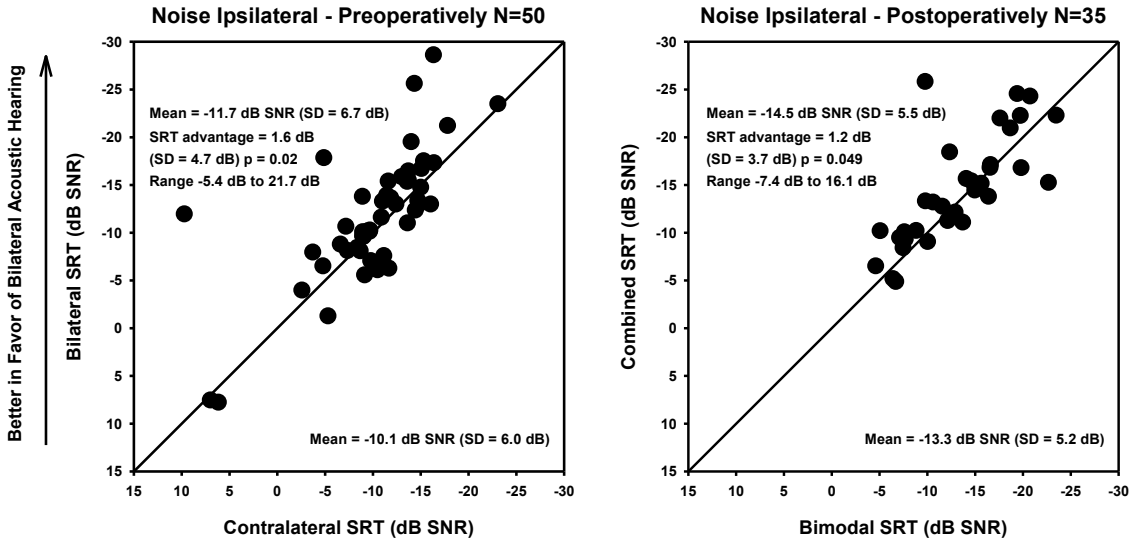

Figure 7: Speech Reception Thresholds (SRT) for listening conditions pre- and postoperatively with noise directed to the implanted ear.

Taking the graph to the left of Figure 7 first, SRTs are plotted for each subject when using Bilateral Acoustic (aided) hearing (Y-axis) as a function of the SRTs obtained for the same subjects when using the Contralateral Acoustic (aided) condition only. So, any improvement resulting from the addition of acoustic hearing in the ipsilateral, implanted ear to contralateral acoustic hearing would be evidenced by points above the diagonal. Bilateral acoustic hearing offered an average SRT advantage of 1.6 dB ($p = 0.02$) over that available when the subject were using the contralateral ear alone. This would be consistent with a squelch effect (i.e., a binaural advantage arising from the addition of a second ear receiving a poorer signal-to-noise ratio). Taking the graph to the right of Figure 7, SRTs are plotted for each subject when using Combined Mode (Y-axis) as a function of the SRTs obtained for the same subjects when using the Bimodal Mode. Again, the results suggest an advantage to the addition of ipsilateral acoustic hearing over

contralateral acoustic hearing alone of 1.2 dB (p = 0.049). Note that data were available for 35 subjects (all but 5 subjects had severe or better levels of low-frequency hearing ipsilaterally) who had sufficient low-frequency hearing to continue use of the Acoustic Component in the implanted ear. Statistical outputs for these analyses can be found in Appendix 40, Tab 15.

5.9.5.9 Self-Assessment Data

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

The Speech, Spatial, and Qualities of Speech Questionnaire or SSQ (Gatehouse & Noble, 2004) was administered as a self-assessment of hearing (dis)abilities across a range of listening situations that fall within three hearing domains. Forty-nine questions address various aspects of hearing: speech hearing (14 questions concerning hearing speech in a variety of listening situations), spatial hearing (17 questions concerning direction, distance and movement of sound and ability to segregate sounds), and sound qualities (18 questions concerning ease of listening, and naturalness, clarity, identification of different speakers, musical pieces and instruments as well as everyday sounds). Each question is scored by the reader using a line marked from 0 through 10, where 0 corresponds to minimal ability and 10 corresponds to complete ability. The line was marked with major ticks at each whole number from 0 through 10, with minor ticks at each unit. The subjects were free to mark anywhere in the line and the tick closest to the mark made by the subject was used to derive the score for each item. A sample of the SSQ can be found as Appendix 6, Tab 3.

As shown in Appendix 41, Tab 16, 50 subjects completed the SSQ preoperatively, 48 completed the SSQ at 6 months postactivation, and 46 completed the SSQ at the 12-month postactivation interval. Results are reported below for each scale separately. A total score for the SSQ at each test interval was also reported, that reflected averaged scores overt the 3 subscales.

5.9.5.9.1.1 Speech Hearing Scale

For the Speech Hearing Scale (Appendix 41, Tab 16):

- Preoperative SSQ scores obtained in the Bilateral Acoustic condition ranged from 0.8 to 6.2, with a mean score of 3.2 (N=50),
- At the 6-month evaluation in the Combined Mode, scores ranged from 0.7 to 8.8 with a mean of 5.4 (N=48[52]), and
- At 12 months, scores in the Combined Mode ranged from 1.4 to 8.8 with a mean of 5.6 (N=46[53]).

Pre-to-postoperative mean differences were significant based on paired t-tests[54] as summarized in Table 16 below.

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[52] [redacted] did not complete the SSQ at the 6-month evaluation before revision to receive a Freedom cochlear implant. [redacted] did not complete the 6-month study endpoint after reimplantation with a Nucleus 5 cochlear implant.

[53] [redacted] and [redacted] did not complete the 12-month evaluations with the Hybrid cochlear implant after receiving traditional cochlear implants. [redacted] withdrew prior to 12 months after being diagnosed with advancing dementia. [redacted] withdrew prior to reaching the 12-month evaluation after being diagnosed with pancreatic cancer.

[54] If there was significant evidence that the assumptions of the t-test were not met (i.e., $p < 0.05$ for a Shapiro-Wilk test of normality), a Wilcoxon signed-rank test was used instead.

Table 16: Pre- to Postoperative Statistical Outcomes for the SSQ – Speech Hearing Scale.

Pre-to-Post Comparison	Change Score Mean ± S.D. (95% C.I)	t (Paired t-test) or S (Signed-Rank Test)	P-Value*
6 Months Postactivation	2.2 ± 1.8 (1.6, 2.7)	t(47) = 8.09	P < 0.0001
12 Months Postactivation	2.3 ± 1.8 (1.7, 2.8)	t(45) = 8.56	P < 0.0001

*Student's t-test p-value; signed-rank p-value if normality assumption failed.

5.9.5.9.1.2 Spatial Hearing Scale

For the Spatial Hearing Scale (Appendix 41, Tab 16):

- Preoperative SSQ scores obtained in the Bilateral Acoustic condition ranged from 1.4 to 9.2, with a mean score of 4.5 (N=50),
- At the 6-month evaluation in the Combined Mode, scores ranged from 1.1 to 8.3 with a mean of 5.5 (N=48), and
- At 12 months, scores in the Combined Mode ranged from 1.6 to 8.5 with a mean of 5.7 (N=46).

Pre-to-postoperative mean differences were significant based on paired t-tests[55] as summarized in Table 17 below.

[55] If there was significant evidence that the assumptions of the t-test were not met (i.e., $p < 0.05$ for a Shapiro-Wilk test of normality), a Wilcoxon signed-rank test was used instead.

Table 17: Pre- to Postoperative Statistical Outcomes for the SSQ – Spatial Hearing Scale.

Pre-to-Post Comparison	Change Score Mean ± S.D. (95% C.I)	t (Paired t-test) or S (Signed-Rank Test)	P-Value*
6 Months Postactivation	0.9 ± 2.0 (0.4, 1.5)	t(47) = 3.27	P < 0.003
12 Months Postactivation	1.1 ± 1.9 (0.5, 1.7)	t(45) = 3.99	P < 0.0003

*Student's t-test p-value; signed-rank p-value if normality assumption failed.

5.9.5.9.1.3 Sound Qualities Scale

For the Sound Qualities Scale (Appendix 41, Tab 16):

- Preoperative SSQ scores obtained in the Bilateral Acoustic condition ranged from 1.6 to 8.1, with a mean score of 5.0 (N=50),
- At the 6-month evaluation in the Combined Mode, scores ranged from 2.7 to 9.1 with a mean of 6.3 (N=48), and
- At 12 months, scores in the Combined Mode ranged from 2.5 to 8.9 with a mean of 6.5 (N=46).

Pre-to-postoperative mean differences were significant based on paired t-tests as summarized in Table 18 below.

Table 18: Pre- to Postoperative Statistical Outcomes for the SSQ – Sound Qualities Scale.

Pre-to-Post Comparison	Change Score Mean ± S.D. (95% C.I)	t (Paired t-test) or S (Signed-Rank Test)	P-Value*
6 Months Postactivation	1.3 ± 2.0 (0.8, 1.9)	t(47) = 4.64	P < 0.0001
12 Months Postactivation	1.5 ± 2.5 (0.8, 2.2)	t(45) = 4.13	P < 0.0003

*Student's t-test p-value; signed-rank p-value if normality assumption failed.

5.9.5.9.1.4 Total SSQ Score

For the Total score (average of the 3 subscales of the SSQ) (Appendix 41, Tab 16):

- Preoperative SSQ scores obtained in the Bilateral Acoustic condition ranged from 1.3 to 7.8, with a mean score of 4.2 (N=50),
- At the 6-month evaluation in the Combined Mode, scores ranged from 2.5 to 8.5 with a mean of 5.7 (N=48), and
- At 12 months, scores in the Combined Mode ranged from 2.5 to 8.4 with a mean of 5.9 (N=46).

Pre-to-postoperative mean differences were significant based on paired t-tests as summarized in Table 19 below.

Table 19: Pre- to Postoperative Statistical Outcomes for the SSQ – Total Scale.

Pre-to-Post Comparison	Change Score Mean ± S.D. (95% C.I)	t (Paired t-test) or S (Signed-Rank Test)	P-Value*
6 Months Postactivation	1.5 ± 1.7 (1.0, 2.0)	t(47) = 5.90	P < 0.0001
12 Months Postactivation	1.6 ± 1.9 (1.1, 2.2)	t(45) = 5.93	P < 0.0001

*Student's t-test p-value; signed-rank p-value if normality assumption failed.

5.9.5.9.2 Device Use Questionnaire (DUQ)

An "in-house" designed device usability metric, the Device Use Questionnaire or DUQ, was administered to determine subjective preferences with regards to device use in various listening environments. It was administered preoperatively, 6 months postactivation, and 12 months postactivation. The preoperative questionnaire contained 93 questions and the postoperative questionnaire contained 95 questions. The majority of the questions were multiple choice. A copy of the DUQ can be found in Appendices 7 and 8, Tab 3. A summary of the results for each question, for each of the test intervals can be found in Appendix 42, Tab 16.

Fifty subjects completed the DUQ preoperatively, 48[56] completed the DUQ at 6 months postactivation, and 46[57] completed the DUQ at the 12-month postactivation interval. A brief summary of responses to some of the key questions posed can be found below.

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[56] [redacted] did not complete the metric due to time constraints. [redacted] was reimplanted prior to the 6-month evaluation.

Preoperative Results:

- Most, 76.0% (38/50), reported the use of bilateral hearing aids as the overall preferred way of listening most of the time.
- When asked to indicate how satisfied they were with their performance in their overall preferred way of listening
    - Most 76.0% (38/50) reported being 'dissatisfied' or 'very dissatisfied,
    - Few, 8.0% (4/50), reported being "satisfied" or "very satisfied".

Postoperative Results:

- Table 20 summarizes the responses when subjects were asked to describe their overall preferred way of listening most of the time since receiving the Nucleus Hybrid Cochlear Implant:

Table 20: Preferred way of listening since receiving the Nucleus Hybrid cochlear implant.

Condition	6 Months Postactivation	12 Month Postactivation
Acoustic Only	N/A	2.2% (1/46)
Bimodal Mode	29.2% (14/48)	19.6% (9/46)
Combined Mode	64.6% (31/48)	65.2% (30/46)
Hybrid Mode	6.3% (3/48)	13% (6/46)

- 80.4% (37/46) reported that it was "very easy" or "moderately easy" to adjust to two different systems (electric and acoustic) at 12 months, compared with 75.0% (36/48) at 6 months;

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[57] [redacted] and [redacted] were reimplanted prior to the 12-month evaluation. [redacted] and [redacted] withdrew from the study prior to the 12-month evaluation.

- Only 8.7% (4/46) reported that it was “moderately difficult” at 12 months, compared with 10.4% (5/48) reporting either the adjustment as “moderately difficult” or “very difficult” at 6 months postactivation.
- Many subjects, 60.9% (28/46), reported that sound was the most pleasant and natural in the Combined Mode at 12 months, compared with 64.6% (31/48) at 6 months;
- 17.4% (8/46) reported the Hybrid Mode; 6.3% (3/48) at 6 months
- 15.2% (7/46) reported the Bimodal Mode; 25.0% (12/48) at 6 months, and
- 6.5% (3/46) reported hearing aids only; 2.1% (1/48) at 6 months.
- The majority of subjects 69.6 (32/46), reported that overall ease of listening was greatest in the Combined Mode at 12 months, compared with 68.8% (33/48) at 6 months;
- 17.4% (8/46) reported the Bimodal Mode provided the greatest overall ease of listening; 27.1% (13/48) at 6 months, and
- 13.0% (6/46) reported the Hybrid Mode providing the greatest overall ease of listening; 4.2% (2/48) at 6 months.
- 78.2% (38/46) subjects reported being “very satisfied” or “satisfied” with their overall performance at 12 months, similar to results at 6 months;
- 17.4% (8/46) reported being “dissatisfied” or “very dissatisfied” with their overall performance at 12 months, compared with 14.6% (7/48) at 6 months.
- 80.4% (37/46) of subjects reported being “very satisfied” or “satisfied” with the decision they made to receive the Nucleus Hybrid Cochlear Implant at 12 months, similar to results at 6 months;
- 6.5% (3/46) reported being “dissatisfied” or “very dissatisfied” with their decision at 12 months, compared with 8.3% (4/48) at 6 months.

The responses summarized above regarding preferred listening mode, sound quality, satisfaction, and adjustment, indicate that subjects can successfully adjust to combined electric and acoustic inputs via the Nucleus Hybrid cochlear implant system.

5.9.5.9.3 Musical Background Questionnaire (MBQ)

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 prior to hearing loss, listening habits, satisfaction with device for music listening, quality of music, enjoyment of musical styles, and enjoyment of different instrumental timbres. Copies of the pre- and postoperative forms of the MBQ can be found in Appendices 9 and 10, Tab 3.

Fifty subjects completed the MBQ preoperatively, and 48[58] completed the questionnaire at 6 months postactivation. A summary of the results for key aspects of the metric is presented below with more complete summaries available in Appendix 43, Tab 16.

Sixteen of the 50 subjects (32%) of the subjects reported being formally trained in music (Question 31, preoperative version). Preoperatively (Question 1), the majority of subjects 36/50 (72%) of the subjects reported preferring to use bilateral hearing aids when listening to music, 11/50 (22%), preferred to use no amplification and 2/50 (4%) preferred to use one hearing aid when listening to music.

Preoperatively, most subjects indicated that music was important to them prior to acquiring hearing loss (Question 34):

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[58] [redacted] did not complete the metric due to time constraints. [redacted] was reimplanted prior to the 6-month evaluation.

- 39/50 (78%) indicated that music was important or very enjoyable before hearing loss, no one indicated avoiding music,
- Only 11/50 (22%) indicated that music was difficult to understand, unimportant or that they never really listened to music.

After acquiring hearing loss these numbers changed, consistent with the negative impact hearing impairment has on music enjoyment. (Question 35):

- Many subjects 37/50 (74%) indicated that music was difficult to understand, unimportant or that they never really listened to music or avoided music,
- Only 13/50 (26%) indicated that music was important or very enjoyable after hearing loss.

At 6 months postactivation, 27/48 (56.3%) reported that music was important to them and enjoyable (Question 5, postoperative). Many of the subjects 36/48 (75.0%) reported that music had improved (Question 10). Most of the subjects reported preferring to listen to music using two ears (Question 1), as they did preoperatively:

- 26/48 (54.2%) reported preferring to use the Combined mode when listening to music,
- 14/48 (29.2%) reported using the Bimodal mode,
- 2/48 (4.2%) reported using the Hybrid mode,
- 2/48 (4.2%) reported using the cochlear implant alone (no acoustic amplification),
- 2/48 (4.2%) reported using one hearing aid alone with no cochlear implant, and
- 2/48 (4.2%) reported using no devices at all when listening to music.

Prior to acquiring hearing loss most (41/50 or 82%) the subjects chose to listen to music 3 hours per week or more (Question 32, preoperative):

- 1/50 (2%) never listened,
- 8/50 (16%) listened less 3 hours per week,
- 13/50 (26%) listened 3-5 hours per week,

- 12/50 (24%) listened 6-8 hours per week,
- 16/50 (32%) listened 9 or more hours per week.

After acquiring hearing loss only half the subjects again reported choosing to listen to music 3 hours per week or more (Question 33, preoperative):

- 5/50 (10%) never listened,
- 22/50 (44%) listened less 3 hours per week,
- 16/50 (32%) listened 3-5 hours per week,
- 4/50 (8%) listened 6-8 hours per week,
- 5/50 (10%) listened 9 or more hours per week.

Of note is that only 18% of the subjects reported listening to music 6 to 8 hours or more per day after hearing loss compared with 56% prior to hearing loss.

After receiving the Hybrid cochlear implant two-thirds of the subjects reported listening to music 3 hours per week or more:

- 16/48 (33.3%) listened less than 3 hours per week,
- 16/48 (33.3%) listened 3-5 hours per week,
- 6/48 (12.5%) listened 6-8 hours per week,
- 10/48 (20.8%) listened 9 or more hours per week.

Although not a return to the levels of listening reported prior to hearing loss, reported preoperatively these data indicated a shift towards more hours of music listening with the Hybrid implant than prior.

Subjects were asked to rate the quality of music, Questions 56 through 63, preoperatively, and 28 through 35, postoperatively. Average ratings are summarized below in Table 21. For the first three scales in the table below a higher score is better. For the remaining five scales, smaller scores indicate better performance.

Table 21: Average ratings for music qualities.

Question (rating from 0 to 10)	Average Preoperative Rating (N=50)	Average Postoperative Rating (N=48)
0 - Empty to 10 - Full	**5.0**	**6.6**
0 – Unpleasant to 10 - Pleasant	**5.6**	**6.4**
0 - Unnatural to 10 – Natural	**5.2**	**6.0**
0 - Clear to 10 Fuzzy	6.8	4.6
0 – Sounds like Music 10 – Does not	4.0	3.9
0 – Complex to 10 - Simple	4.3	4.5
0 – Easy to Follow to 10 - Difficult	5.7	4.5
0 – Like sound of music very much to 10 - Dislike	3.3	3.3

As shown by the responses summarized above, recipients on average chose to listen to music more following implantation with the Hybrid cochlear implant. Overall ratings of sound quality shown in Table 21 rated music as more favorable in most comparisons. The majority of recipients choose to listen to music in an electric-acoustic mode, indicating that subjects could integrate the two types of signals for important non-speech stimuli such as music.

5.9.6 Acoustic Hearing Sensitivity Outcomes

Pre- and postoperative hearing threshold data through the individual subject test intervals, are available. Audiometric threshold data (air and bone conduction) for both the ipsilateral, implanted ear (Appendix 44) and the contralateral ear (Appendix 45) are provided in Tab 17 for all subjects with respective test intervals. Appendices 46 and 47 in the same Tab show the ipsilateral and contralateral low-frequency threshold *difference*

scores for postoperative minus the preoperative interval, and the calculated low-frequency average difference (125 Hz through 1000 Hz, inclusively), respectively.

In the appended data, all audiometric thresholds are reported in dB HL. However, please note that in our automated database system, both air- and bone-conduction vibrotactile responses are reported in the appended data as 131 dB and no responses (at the maximum output of the equipment) are reported as 132 dB in the appendices.

5.9.6.1 Pre-to-Postoperative Changes in Low-Frequency Hearing Sensitivity (Averaged over 125 through 1000 Hz)

Figure 8 plots the preoperative unaided air conduction thresholds for the implanted ear, with the shaded region representing the range of audiometric profiles fitting the selection criterion for the study. As shown, subjects typically presented with normal through moderate levels of hearing loss up to 750 Hz, sloping to severe or profound high-frequency hearing loss.

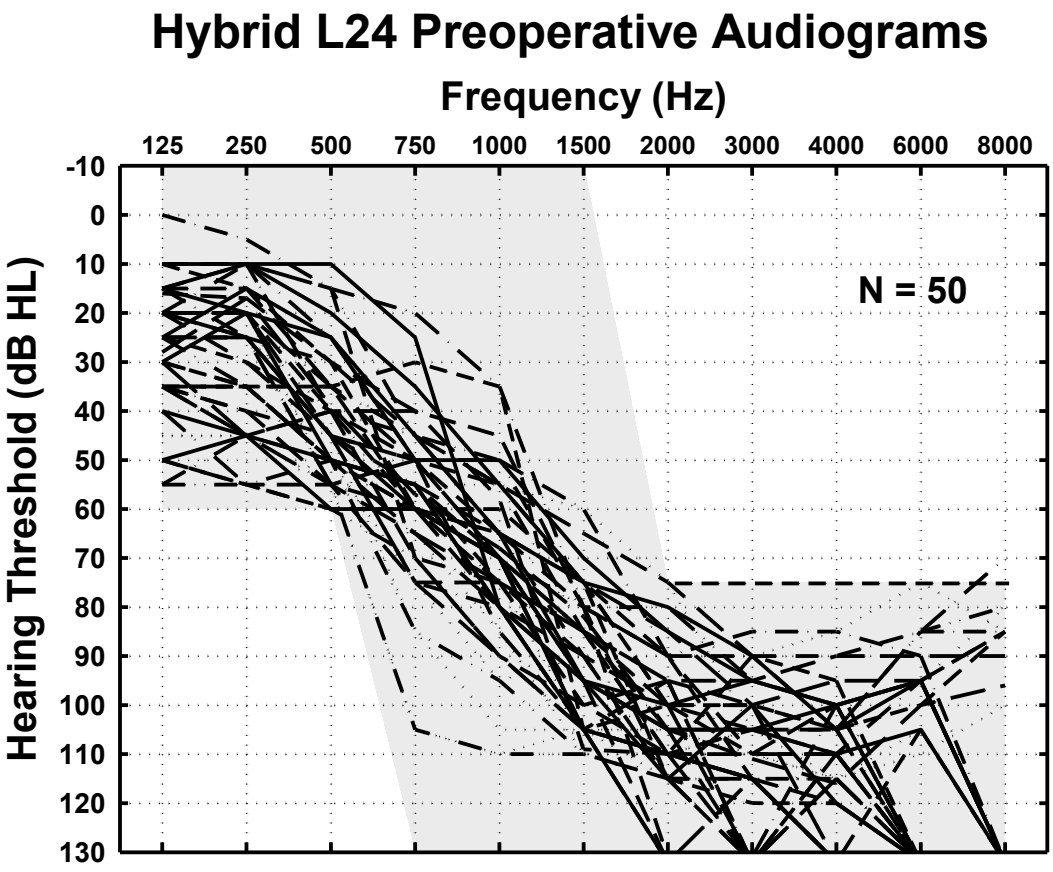

Figure 8: Preoperative audiometric thresholds (air conduction) for the implanted ear (N=50).

5.9.6.1.1 Six-Month Endpoint

Forty-eight[59] subjects completed audiometric assessments for the 6-month postactivation primary endpoint. The following summarizes changes observed in low-frequency hearing

[59] [redacted], evaluated at 3 months with a profound loss of hearing was not assessed audiometrically at 6 months (but was assessed for efficacy). Subject [redacted], also evaluated at 3 months with a profound loss of hearing, was reimplanted prior to the 6-month evaluation.

(averaged over the range 125 through 1000 Hz) pre- to postoperatively for individual subjects by the 6-month interval.

At 6 months postactivation:

- 12/48 (25%) subjects experienced a decrease in low-frequency hearing averaged over the range 125 through 1000 Hz $\leq$ 10 dB postoperatively compared with preoperatively,
- 24/48 (50%) subjects experienced a decrease in low-frequency hearing averaged over the range 125 through 1000 Hz $\leq$ 20 dB,
- 27/48 (56.3%) subjects experienced a decrease in low-frequency hearing averaged over the range 125 through 1000 Hz $\leq$ 30 dB, and
- 21/48 (43.8%) subjects experienced a decrease in low-frequency hearing averaged over the range 125 through 1000 Hz > 30 dB at 6 months relative to the preoperative status.

The following summarizes the number of subjects falling within various degrees of low-frequency hearing sensitivity (averaged over the range 125 through 1000 Hz).

At 6 months postactivation:

- 15/48 (31.3%) subjects experienced a moderate (41 through 55 dB HL) low-frequency hearing loss over the range 125 through 1000 Hz by the 6-month postactivation interval,
- 9/48 (18.8%) subjects experienced a moderately severe (56 through 70 dB HL) low-frequency hearing loss over the range 125 through 1000 by the 6-month postactivation interval,
- 9/48 (18.8%) subjects experienced a severe (71 through 90 dB HL) low-frequency hearing loss over the range 125 through 1000 by the 6-month postactivation interval,

- 10/48 (20.8%) subjects experienced a profound (>90 dB HL) low-frequency hearing loss over the range 125 through 1000 Hz by the 6-month postactivation interval,
- 5/48 (10.4%) subjects experienced a total loss of low-frequency hearing loss over the range 125 through 1000 Hz by the 6-month postactivation interval.

5.9.6.1.2 Hearing Sensitivity Outcomes Over Time

5.9.6.1.2.1 Change in Low-Frequency (Pure-Tone Average of 125 through 1000 Hz) Hearing

Appendix 48 in Tab 17 provides individual and summary data concerning pre- to postoperative changes in low-frequency hearing over time. Over the entire study period (not just the endpoint of 6 months), 30 of 50 subjects experienced changes in low-frequency hearing of more than 30 dB, at a minimum of one test interval. Five of these cases improved such that LF thresholds were within 30 dB of preoperative levels [redacted] and [redacted] as of the most recent evaluation for each subject. All were considered 'Resolved' (change in hearing no longer > 30 dB and observed over two or more evaluations) as of the writing of this report.

At 12 months postactivation:

- 9/46[60] (19.6%) subjects experienced a decrease in low-frequency hearing averaged over the range 125 through 1000 Hz ≤ 10 dB postoperatively compared with preoperatively,

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[60] [redacted] and [redacted] experienced a profound loss of hearing and were reimplanted before 12 months postactivation. [redacted] withdrew prior to 12 months after being diagnosed with pancreatic cancer. [redacted] withdrew prior to 12 months after being diagnosed with the onset of dementia.

- 21/46 (45.7%) subjects experienced a decrease in low-frequency hearing averaged over the range 125 through 1000 Hz $\leq$ 20 dB,
- 27/46 (58.7%) subjects experienced a decrease in low-frequency hearing averaged over the range 125 through 1000 Hz $\leq$ 30 dB, and
- 21/46 (41.3%) subjects experienced a decrease in low-frequency hearing averaged over the range 125 through 1000 Hz > 30 dB at 6 months relative to the preoperative status.

By the 12-month interval, the percentage of subjects who retained severe or better levels of hearing remained consistent with that observed at the 6-month interval. This was also true for subjects with data available out to 24 months postactivation. The number of subjects with follow-up data beyond 24 months makes conclusions regarding further changes in hearing beyond this time period difficult.

5.9.6.1.2.2 Degree of Low-Frequency (Pure-Tone Average of 125 through 1000 Hz) Hearing

Appendix 49 in Tab 17 provides individual and summary data concerning the degree of pre- and postoperative low-frequency hearing over time. Over the entire study period (not just the endpoint of 6 months), 22 of 50 subjects experienced changes in low-frequency hearing resulting profound or total loss of hearing.

At 12 months postactivation:

- 15/46 (32.6%) subjects experienced a moderate (41 through 55 dB HL) low-frequency hearing loss over the range 125 through 1000 Hz,
- 10/46 (21.7%) subjects experienced a moderately severe (56 through 70 dB HL) low-frequency hearing loss over the range 125 through 1000 Hz,
- 8/46 (17.4%) subjects experienced a severe (71 through 90 dB HL) low-frequency hearing loss over the range 125 through 1000 Hz,
- 8/46 (17.4%) subjects experienced a profound (>90 dB HL) low-frequency hearing loss over the range 125 through 1000 Hz,

- 5/46 (10.9%) subjects experienced a total loss of low-frequency hearing loss over the range 125 through 1000 Hz.

Figure 9 and Figure 10 plot individual changes in low-frequency hearing as a function of time for all available data as of this report. Each panel within the figure plots data based on the onset of change in hearing. Twenty-five subjects with changes of more than 30 dB that occurred prior and up to and including the 12-month postactivation period are plotted in the first four panels. These graphs illustrate that such changes typically occur within the first 3 to 6 months following device activation (21 of 25 subjects experienced such changes by 6 months postactivation). The fifth panel shows 5[61] subjects who experienced changes in hearing but improved (i.e., hearing within 30 dB of preoperative level) with the sixth panel showing those 20 subjects who did not experience significant changes (i.e., < 30 dB) in hearing. What is remarkable about these subjects, particularly the latter group, is that low-frequency hearing appears to remain quite stable even out to 42 to 48 months postactivation.

5.9.6.2 Factors Related to Loss of Acoustic Sensitivity

It was interest to examine whether or not there were any predictive factors related to postoperative changes in hearing sensitivity. Appendices 50 and 51, Tab 18 contain 6-month hearing sensitivity data (for change in low-frequency hearing pre- to postoperatively and degree of hearing loss) subgrouped based on the following baseline characteristics:

1) Gender (i.e., males vs. females).
2) Median age at implantation (i.e., < 68 years or ≥ 68 years).
3) Median duration of hearing loss (i.e., < 23.5 years or ≥ 23.5 years).

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[61] Subjects [redacted] and [redacted] experienced middle-ear issues that resolved and may explain the improvement observed.

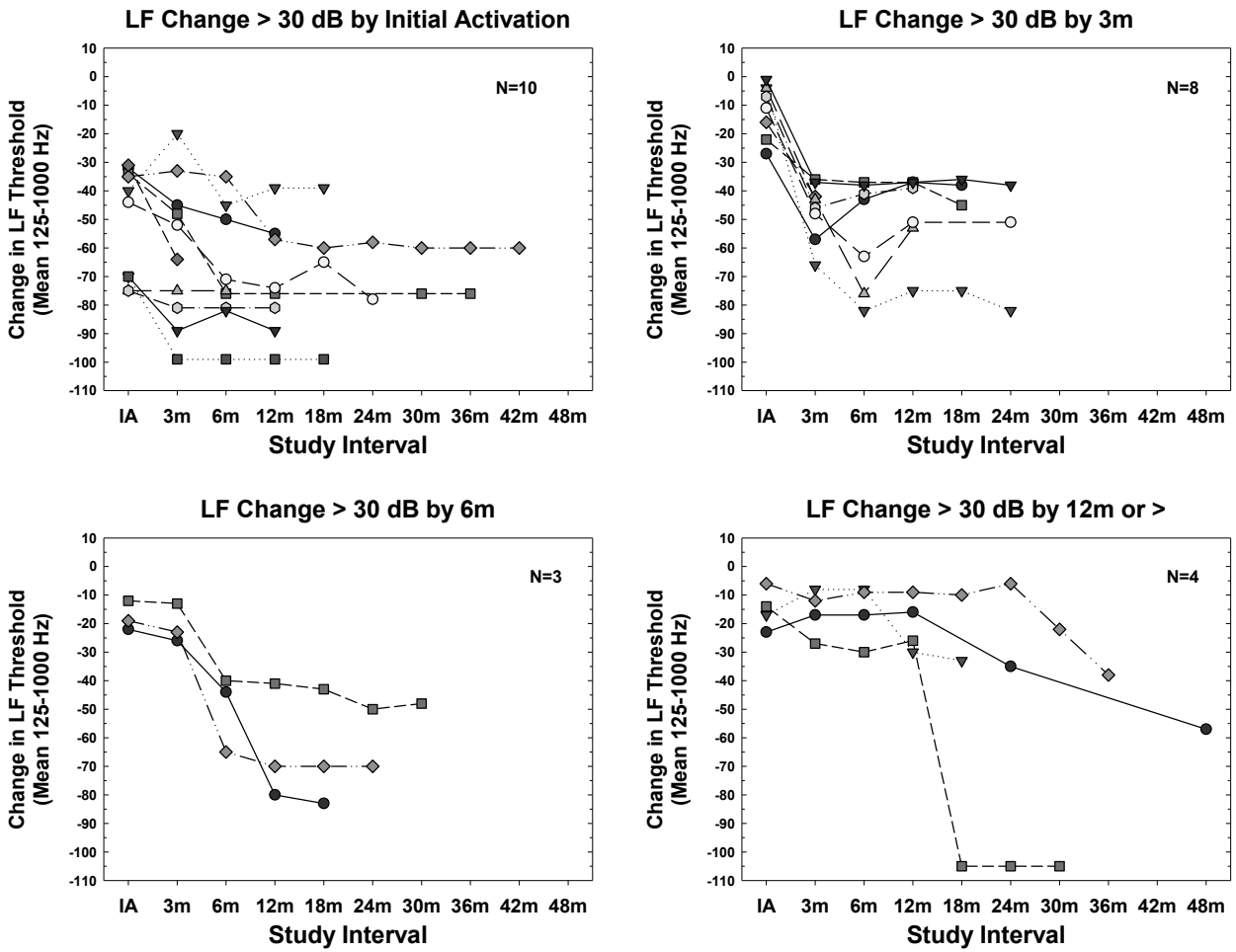


Figure 9: Change in low-frequency (average of 125 through 1000 Hz) over time for individual subject with the Hybrid L24 implant.

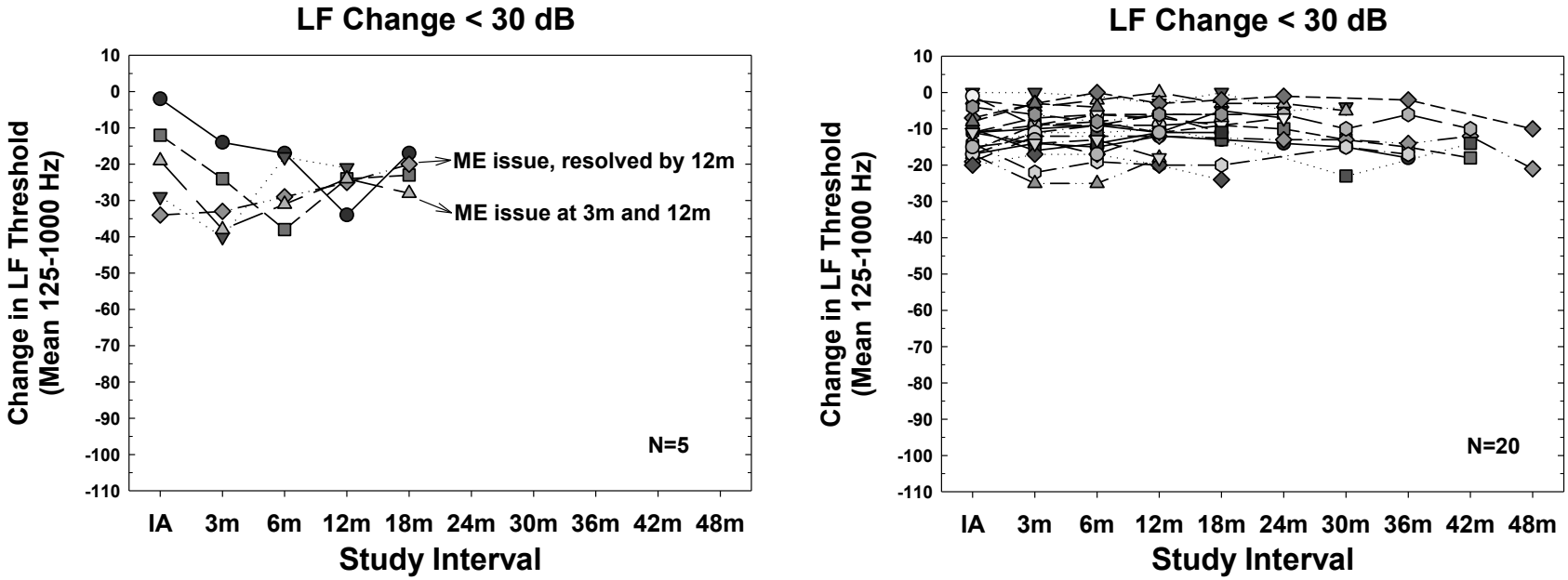


Figure 10: Change in low-frequency (average of 125 through 1000 Hz) over time for individual subject with the Hybrid L24 implant (improved or < 30 dB HL).

4) Median duration of severe to profound high-frequency hearing loss (i.e., < 21.7 years or ≥ 11.7 years).
5) Etiology of hearing loss.
6) Median preoperative baseline scores for CNC (< 24% years or ≥ 24%) and AzBio(< 14.2% years or ≥ 14.2%) in the ipsilateral, Acoustic Alone condition.

Results indicated that gender was a factor in determining hearing sensitivity outcomes based on these comparisons. This was not the case for age at implantation, duration of overall hearing loss, duration of severe to profound high-frequency hearing loss, etiology of hearing loss, and baseline speech scores. The mean change in low-frequency hearing (LFHL) was 22.6 dB at 6 months postactivation for females, significantly less than that observed for males, 42.2 dB (p = 0.01), as shown in Table 22 below. The mean degree of low-frequency hearing loss (averaged over 125 through 1000 Hz) for females was 67 dB HL (moderate to severe) compared with 87.8 dB HL (severe).

Table 22: Subgroup analyses of baseline characteristics effects on 6-Month hearing sensitivity outcomes.

Outcome Measure	Gender P-value*	Age P-value*	Duration of Loss P-value*	Duration of Severe to Profound HF Loss P-value*	Etiology P-value*	Baseline CNC Score P-value*	Baseline AzBio Score P-value*
Change LFHL	0.01	0.16	0.722	0.275	0.97	.45	.9
Degree LFHL	0.016	0.088	0.536	0.581	0.949	.91	.879

*ANOVA p-value.

5.9.6.3 Data Compared and Contrasted Across Hybrid Studies

As described in the literature review, there have been a number of clinical studies in the U.S. and Europe that have involved Cochlear Nucleus devices with somewhat different electrode array designs. Across these studies more than 200 subjects have been implanted providing an opportunity to explore the incidence and pattern of hearing preservation across a large group of subjects. At the same time, it needs to be recognized that the various Nucleus devices studied have involved electrode arrays of different lengths (primarily 10 and 16 mm designs) with different numbers of electrode contacts, two insertion techniques (cochleostomy vs. round-window), and different subject demographics. What follows is a summary of analyses in which hearing sensitivity data were compared and contrasted across U.S. and European based Nucleus Hybrid cochlear implant studies.

Available data from U.S. studies involving the Nucleus Hybrid S8 (N=87), Hybrid S12 (N=24), and the Hybrid L24 (N=50) were considered along with data from a European-based trial of the Hybrid L24 (N=66), yielding a total 227 subjects. Tab 19 contains the demographic information (Appendix 52) for these subjects along with hearing sensitivity data for the treated ear in Appendices 53 (pre- to postoperative changes) and 54 (degree of low-frequency hearing loss) . Statistical analysis outputs can be found under Appendix 55, Tab 19.

Key demographic characteristics for the three device/study groups are summarized in Table 23. Demographics for the U.S. study groups appear to be quite similar. However, the European study group appear to be quite different; most notably with regards to age at implantation (6.5 to 10.6 years younger on average) and the distribution of gender. The U.S. study groups had close to a 50/50 split, proportionally, between Females and Males. However, 72.7% of the European group were Female and 19.7% Male (7.5% were unspecified). There are differences with regards to duration of hearing loss, though this is

likely related to the age differences (younger subjects will naturally have shorter durations of hearing loss.

Table 23: Demographic summary of the U.S. and European Hybrid study groups.

Demographic Characteristic	US Hybrid L24 N=50	U.S. Hybrid S8/S12 N=111	EU Hybrid L24 N=66
Mean Age at CI (S.D.)	64.1 yrs. (14.7 yrs.) Range: 23 – 86.2 yrs.	60.0 yrs. (14.1 yrs.) Range: 19.6 – 86.8 yrs.	53.5 yrs. (12.7 yrs.) Range: 21.5 – 81.8 yrs.
Gender	Males: 25 Females: 25	Males: 52 Females: 59	Males: 13 Females: 48 Unknown: 5
Ear Implanted	Left: 24 Right: 26	Left: 50 Right: 61	Left: 31 Right: 35
Mean Duration of Overall HL	28.1 yrs. (14.9 yrs.)	26.4 yrs. (13.3 yrs.)	19.4 yrs. (15.7 yrs.)
Mean Duration of SP HL	13.1 yrs. (7.2 yrs.)	15.3 yrs. (10.4 yrs.)	7.0 yrs. (12.3 yrs.)

It was of interest to examine the level of low-frequency hearing preservation in terms of the pre- to postoperative changes observed in addition to the degree of low-frequency hearing loss maintained for the different devices/studies. It is important to note that the low-frequency pure-tone averages (PTA) were calculated somewhat differently than those reported for the U.S. Hybrid L24 subjects. The European protocol did not require the measurement of hearing thresholds for 125 and 750 Hz. Consequently, to make the U.S. and European datasets comparable, the low-frequency PTA (for change and degree values) were made based on thresholds available for 250, 500, and 1000 Hz. In addition, although data are available for the U.S. Hybrid L24 study beyond 12 months there was a lack of such data for the other studies, particularly for the European study, where no data

was available beyond 12 months postactivation. Hence, comparisons were made across devices/studies for data within this 12-monht time period.

Table 24 provides summary statistics of the pre- to postoperative changes observed in low-frequency hearing sensitivity across the different device types. The Hybrid S8 and S12 data were pooled given that the arrays were dimensionally equivalent and involved the same surgical technique for insertion. Table 25 provides summary statistics for the degree of postoperative low-frequency hearing observed at each interval up to 12 months across the various devices. On average, the subjects presented with severe (71 through 90 dB HL) levels of low-frequency hearing loss postoperatively although the degree of change in low-frequency thresholds differed somewhat across the studies presented. That is, the mean changes observed for the U.S. Hybrid L24 subjects appeared to be somewhat larger, and the confidence intervals nonoverlapping, when compared with the European Hybrid L24 subjects and the U.S. Hybrid S8/S12 subjects (Table 24). However, the degree of low-frequency hearing loss during follow-up (i.e., where the subjects "ended up" hearing wise) resulting from these changes appeared to be similar, on average, across the 3 device groups evidenced by the overlapping confidence intervals (Table 25).

Appendix 55, Tab 19 tabulates the mean changes in low-frequency hearing observed between study intervals for each device/study group. These data suggest that the largest changes in low-frequency hearing occurred between the preoperative interval (0 month) and initial activation (1-month postactivation), with smaller and less consequential inter-evaluation changes occurring thereafter. For example, in the U.S. Hybrid L24 study low-frequency hearing thresholds (PTA of 250, 500, and 1000 Hz) changed by 21 dB (i.e., low-frequency hearing loss increased) between the preoperative evaluation and device activation, 1-month postoperatively. By the 3-month evaluation, low-frequency hearing decreased an additional 8.8 dB on average, with less change evident between 3 and 6 months (2.9 dB) and between 6 and 12 months (1.8 dB).

So that incidence of hearing loss could be calculated and compared across device/study groups, the groups were dichotomized based on change in hearing pre- to postoperatively. That is, subjects within each group were divided into two subgroups based on low-frequency threshold changes ≤ 30 dB (unlikely to impact functional low-frequency hearing) and changes > 30 dB (likely to impact functional low-frequency hearing). Appendix 55, Tab 19 presents several summary tables that provide the frequency distributions of hearing loss based on the change values as well as by degree of hearing loss, for initial activation (1 month postoperative) and for 3, 6, and 12 months postactivation.

Table 24: Summary statistics for changes in low-frequency hearing (PTA 250, 500, & 1000 Hz) observed over time for European Hybrid L24 subjects and U.S. Hybrid L24 and Hybrid S8/S12 subjects.

Device Type	Total N	Interval	N	Mean Change (dB)	S.D. (dB)	Lower 95% CL for Mean (dB)	Upper 95% CL for Mean (dB)
EU-L24	66	1m	66	11.8	12.0	8.9	14.8
		3m	65	13.6	15.8	9.7	17.5
		6m	64	15.1	16.9	10.8	19.3
		12m	61	19.4	20.8	14.1	24.7
US-L24	50	1m	50	21.0	18.5	15.7	26.2
		3m	50	29.7	23.2	23.1	36.3
		6m	48	31.7	25.2	24.3	39.0
		12m	46	33.1	26.2	25.3	40.9
US-S8/S12	111	1m	111	13.9	13.7	11.4	16.5
		3m	106	20.3	21.3	16.2	24.4
		6m	105	19.9	20.5	15.9	23.9
		12m	97	20.9	21.1	16.6	25.1

Table 25: Summary statistics for the degree of low-frequency hearing (PTA 250, 500, & 1000 Hz) observed over time for European Hybrid L24 subjects and U.S. Hybrid L24 and Hybrid S8/S12 subjects.

Device Type	Total N	Interval	N	Mean Degree (dB HL)	S.D. (dB)	Lower 95% CL for Mean (dB)	Upper 95% CL for Mean (dB)
EU-L24	66	1m	66	71.7	15.9	67.8	75.6
		3m	65	73.8	20.3	68.8	78.9
		6m	64	75.1	20.8	69.9	80.3
		12m	61	79.5	24.6	73.2	85.8
US-L24	50	1m	50	68.2	20.0	62.5	73.9
		3m	50	77.0	25.7	69.7	84.3
		6m	48	78.6	28.6	70.3	86.9
		12m	46	79.8	29.1	71.2	88.5
US-S8/S12	111	1m	111	64.8	17.5	61.5	68.1
		3m	106	71.4	23.2	66.9	75.9
		6m	105	70.9	23.4	66.4	75.4
		12m	97	71.8	23.7	67.0	76.6

Multivariable logistic regression models (statistical outputs are available in Appendix 55, Tab 19) were fit to measure the odds of acquiring a change in hearing level > 30 dB by 6 months postactivation (endpoint for this study). Two separate models were fit. The first model was adjusted for by age at implantation, gender, and duration of hearing loss. The second model fit was adjusted for by age at implantation, gender, duration of hearing loss, and device type. Of specific interest was whether or not demographic characteristics might have an association with the outcome. This analysis indicated that age at implantation and gender may be related to change in low-frequency hearing. The gender effect held even after adjusting for device type. That is, the analyses indicated that females present with a lower incidence of changes in hearing > 30 dB. This is in line with analyses described above for the U.S. Hybrid L24 data set alone. The chance of acquiring hearing changes > 30 dB did appear to be lower in both the European Hybrid L24 and Hybrid S8/S12 studies when compared with the U.S. Hybrid L24 data but the

demographic and design differences observed make firm conclusions regarding differences across devices/study types problematic.

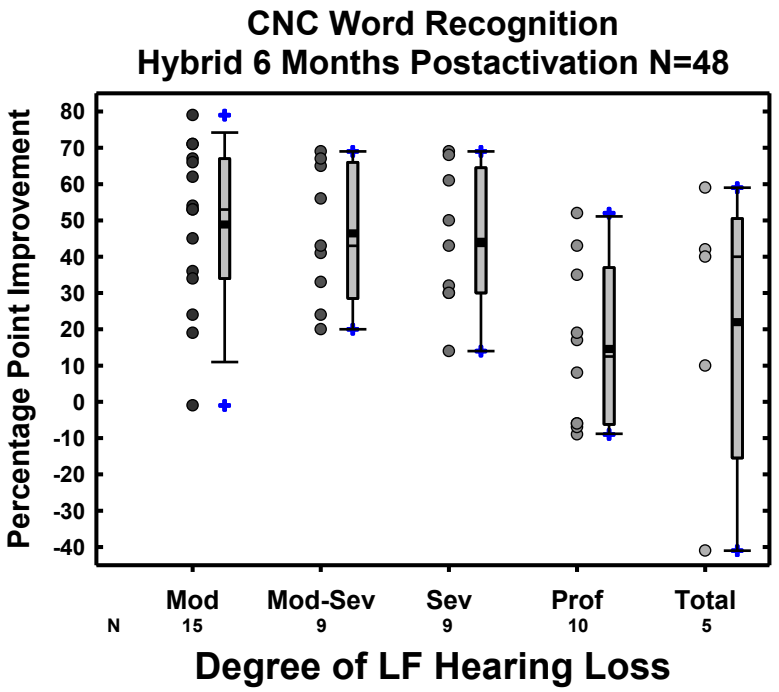
5.9.7 Subgroup Analyses

5.9.7.1 Efficacy Outcomes as a Function of Low-Frequency Hearing Sensitivity

Figure 11 plots the individual pre- and 6-month postactivation CNC and AzBio in noise scores for the treated ear (i.e., Acoustic Alone preoperatively and Hybrid Mode postoperatively) as a function of the degree of low-frequency hearing loss at the 6-month endpoint. Vertical box plots display the mean (thick horizontal line) and median (thin horizontal line) values along with inter-quartile ranges. Statistical analysis (ANOVA) showed a significant effect for degree of hearing loss. That is, pre- to postoperative improvement did depend on the degree of hearing maintained at the 6-month postactivation interval. Results suggested that significant improvement in speech perception is possible for all levels of hearing loss, most particularly for those subjects who maintained severe or better levels of hearing at the 6-month endpoint. Although displayed graphically for the 6-month endpoint in Figure 11, statistical analyses of the 3 and 12-month speech perception data with the subjects subgrouped in the same way (i.e., based on the degree of low-frequency hearing at 6 months) indicated the same pattern of results as shown for the 6-month data. Statistical outputs are available in Appendix 56, Tab 20.

It is also important to consider that the subjects use the Hybrid cochlear implant in concert with acoustic hearing in *both* ears. That is, the normal use mode for the device is the Combined Mode, not the Hybrid Mode. As shown in Figure 12, significant improvement was observed for the subjects using the Combined Mode when compared with the preoperative Bilateral Acoustic condition across all degrees of postoperative low-frequency (PTA of 125 through 100 Hz) hearing levels. 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, when compared with the Bilateral Acoustic condition, preoperatively.



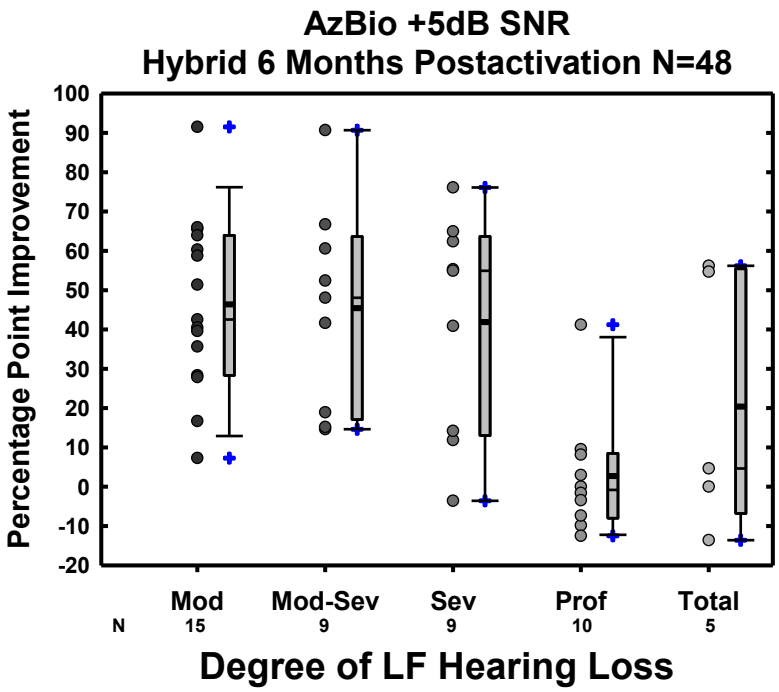


Figure 11: Pre- to 6-Month postactivation Hybrid Mode outcomes for the CNC Word Test (Upper) and AzBio in Noise Test (Lower), as a function of degree of hearing loss at the 6-Month endpoint. Boxes enclose the interquartile ranges, the whiskers bound the 10th and 90th percentiles, with 5th and 95th percentiles indicated by the plus symbols.

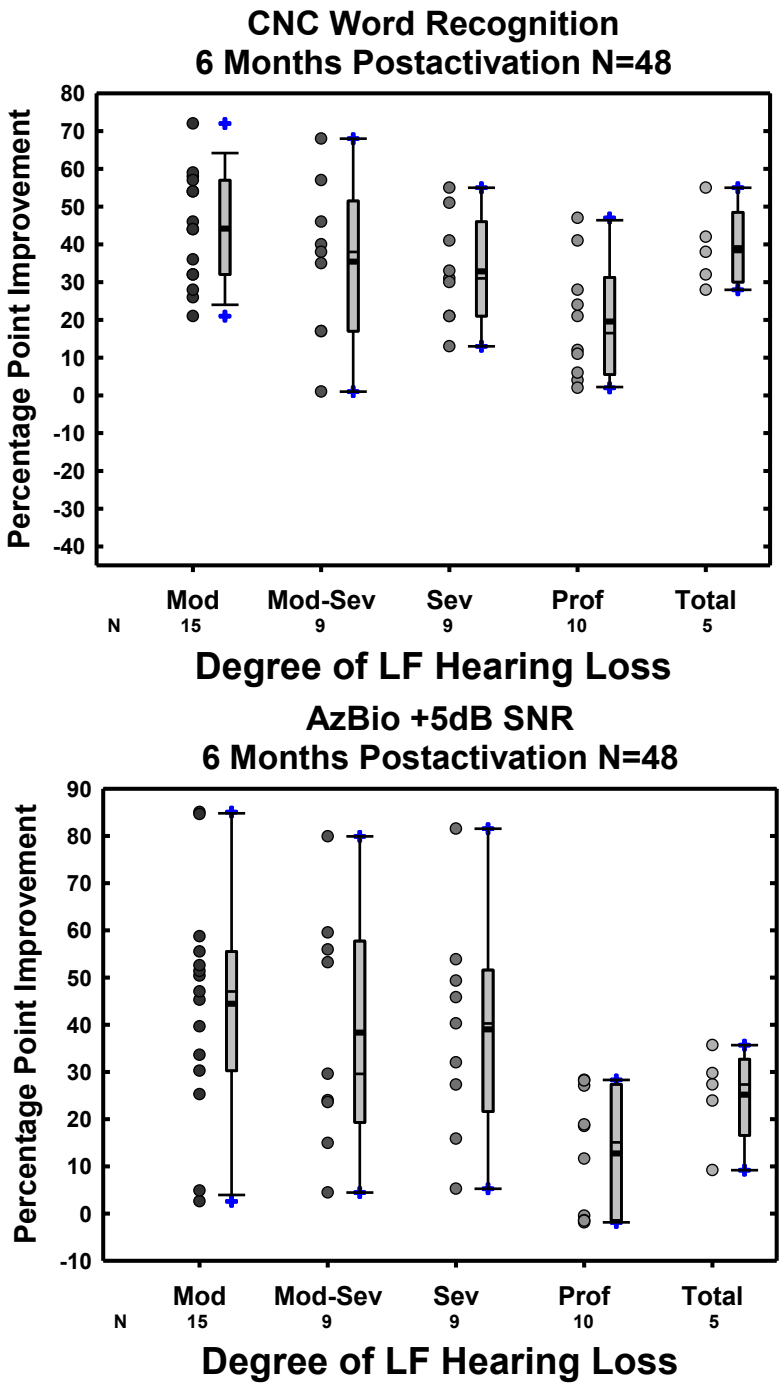


Figure 12: Pre- to 6-Month postactivation Combined Mode outcomes for the CNC Word Test (Upper) and AzBio in Noise Test (Lower), as a function of degree of hearing loss at the 6-Month endpoint. Boxes enclose the interquartile ranges, the whiskers bound the 10th and 90th percentiles, with 5th and 95th percentiles indicated by the plus symbols.

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

Appendix 56, Tab 20 provides the statistical outputs for the UW-CAMP regarding outcomes as a function of the degree of hearing loss. There was an effect of hearing loss on outcomes for the treated ear. As with the speech scores, above, scores for the UW-CAMP were generally very good for subjects with no more than a severe degree of hearing loss and poorer for those with profound or total loss of hearing. Based the on the outcomes for the speech perception tests and the UW-CAMP, the groupings based on degree of hearing loss were collapsed into two groups for summary purposes for the narrative that follows:

- Subjects with severe low-frequency hearing loss or better,
- Subjects with profound or total loss of hearing.

5.9.7.2.1 Pitch Discrimination Subtest – Severe Hearing Loss or Better

5.9.7.2.1.1 Ipsilateral Condition

Appendix 57, Tab 20 provides the raw data for the Pitch Discrimination subtest of the UW-CAMP for those with severe hearing loss or better.

For the 32 subjects with severe low-frequency hearing loss or better:

- Average preoperative pitch discrimination thresholds obtained Acoustic Alone, with a hearing aid in the ipsilateral ear (i.e., the ear to be implanted), ranged from 0.5 to 4.3 semitones, with a mean of 1.2 semitones,
- At the 6 month postactivation test interval, performance in the Hybrid Mode (i.e., Cochlear Implant + Ipsilateral Acoustic) ranged from 0.5 to 3.6 semitones, with a mean of 1.0 semitones.

5.9.7.2.1.2 Bilateral Condition

For the 31[62] subjects with pre- and postoperative data:

- Average preoperative pitch discrimination thresholds obtained in the Bilateral Acoustic condition, with bilateral hearing aids, ranged from 0.5 to 6.3 semitones, with a mean of 1.0 semitones,
- At the 6 month postactivation test interval, performance in the Combine Mode (i.e., Cochlear Implant + Bilateral Acoustic) ranged from 0.5 to 3.7 semitones, with a mean of 1.0 semitones.

5.9.7.2.2 Melody Recognition Subtest – Severe Hearing Loss or Better

Appendix 58, Tab 20 provides the raw data for the Melody subtest of the UW-CAMP for those with severe hearing loss or better.

5.9.7.2.2.1 Ipsilateral Condition

For the 32 subjects with pre- and postoperative data:

- Preoperative melody recognition scores obtained Acoustic Alone ranged from 13.9% to 100%, with a mean of 74.7%,
- At the 6 month postactivation test interval, performance in the Hybrid Mode ranged from 13.9% to 100%, with a mean of 76.4%.

5.9.7.2.2.2 Bilateral Condition

For the 31[63] subjects with pre- and postoperative data:

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[62] [redacted] did not have a score available for the Combined Mode; results not saved due a software error.

[63] [redacted] did not have a score available for the Combined Mode; results not saved due a software error.

- Preoperative melody recognition scores obtained in the Bilateral Acoustic condition ranged 13.9% to 100%, with a mean of 74.0%,
- At the 6 month postactivation test interval, performance in the Combined Mode ranged from 19.4% to 100%, with a mean of 75.5%.

5.9.7.2.3 Timbre Recognition Subtest – Severe Hearing Loss or Better

Appendix 58, Tab 20 provides the raw data for the Timbre subtest of the UW-CAMP for those with severe hearing loss or better.

5.9.7.2.3.1 Ipsilateral Condition

For the 32 subjects with pre- and postoperative data:

- Preoperative timbre recognition scores obtained Acoustic Alone ranged from 33.3% to 91.7%, with a mean of 55.3%,
- At the 6 month postactivation test interval, performance in the Hybrid Mode ranged from 8.3% to 100%, with a mean of 62.1%.

5.9.7.2.3.2 Bilateral Condition

For the 31[64] subjects with pre- and postoperative data:

- Preoperative timbre recognition scores obtained in the Bilateral Acoustic condition ranged 20.8% to 58.3%, with a mean of 59.2%,
- At the 6 month postactivation test interval, performance in the Combined Mode ranged from 25.0% to 91.7%, with a mean of 62.5%.

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[64] [redacted] did not have a score available for the Combined Mode; results not saved due a software error.

5.9.7.2.4 Pitch Discrimination Subtest – Profound or Total Loss of Hearing

5.9.7.2.4.1 Ipsilateral Condition

Appendix 59, Tab 20 provides the raw data for the Pitch Discrimination subtest of the UW-CAMP for those with profound or total loss of hearing.

For the 14[65] subjects with profound or total loss hearing loss:

- Average preoperative pitch discrimination thresholds obtained Acoustic Alone, with a hearing aid in the ipsilateral ear (i.e., the ear to be implanted), ranged from 0.5 to 4.8 semitones, with a mean of 1.2 semitones,
- At the 6 month postactivation test interval, performance in the Hybrid Mode[66] (i.e., Cochlear Implant + Ipsilateral Acoustic) ranged from 0.5 to 8.9 semitones, with a mean of 2.5 semitones.

5.9.7.2.4.2 Bilateral Condition

For the 15 subjects with pre- and postoperative data:

- Average preoperative pitch discrimination thresholds obtained in the Bilateral Acoustic condition, with bilateral hearing aids, ranged from 0.5 to 5.4 semitones, with a mean of 1.3 semitones,
- At the 6 month postactivation test interval, performance in the Combine Mode (i.e., Cochlear Implant + Bilateral Acoustic) ranged from 0.5 to 2.2 semitones, with a mean of 1.2 semitones.

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[65] [redacted] did not have a score available for the Hybrid Mode; results not saved due a software error.

[66] Note that for subjects [redacted] the Hybrid Mode was not tested at 6 months as the best unilateral listening mode because the subjects experienced profound or total loss of hearing and did not derive benefit from the Acoustic Component of the Hybrid device. Thus, preoperative Acoustic Alone scores were compared with the postoperative Hybrid Mode as the best unilateral listening condition.

5.9.7.2.5 Melody Recognition Subtest – Profound or Total Loss of Hearing

Appendix 60, Tab 20 provides the raw data for the Melody subtest of the UW-CAMP for those with profound or total loss of hearing.

5.9.7.2.5.1 Ipsilateral Condition

For the 15 subjects with pre- and postoperative data:

- Preoperative melody recognition scores obtained Acoustic Alone ranged from 11.1% to 88.9%, with a mean of 53.5%,
- At the 6 month postactivation test interval, performance in the Hybrid Mode[67] ranged from 11.1% to 88.9%, with a mean of 43.5%.

5.9.7.2.5.2 Bilateral Condition

For the 15 subjects with pre- and postoperative data:

- Preoperative melody recognition scores obtained in the Bilateral Acoustic condition ranged 16.7% to 97.2%, with a mean of 55.2%,
- At the 6 month postactivation test interval, performance in the Combined Mode ranged from 16.7% to 77.8%, with a mean of 48.3%.

5.9.7.2.6 Timbre Recognition Subtest – Profound or Total Loss of Hearing

Appendix 60, Tab 20 provides the raw data for the Timbre subtest of the UW-CAMP for those with profound or total loss of hearing.

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[67] Note that for subjects [redacted] the Hybrid Mode was not tested at 6 months as the best unilateral listening mode because the subjects experienced profound or total loss of hearing and did not derive benefit from the Acoustic Component of the Hybrid device. Thus, preoperative Acoustic Alone scores were compared with the postoperative Hybrid Mode as the best unilateral listening condition.

5.9.7.2.6.1 Ipsilateral Condition

For the 15 subjects with pre- and postoperative data:

- Preoperative timbre recognition scores obtained Acoustic Alone ranged from 12.5% to 70.8%, with a mean of 43.7%,
- At the 6 month postactivation test interval, performance in the Hybrid Mode[68] ranged from 20.8% to 79.2%, with a mean of 45.0%.

5.9.7.2.6.2 Bilateral Condition

For the 31[69] subjects with pre- and postoperative data:

- Preoperative timbre recognition scores obtained in the Bilateral Acoustic condition ranged 12.5% to 79.2%, with a mean of 52.8%,
- At the 6 month postactivation test interval, performance in the Combined Mode ranged from 20.8% to 79.2%, with a mean of 45.6%.

5.9.7.3 Self-Assessment Data

Of the 50 subjects who completed the Self-Assessment Questionnaires preoperatively, 15 of the 50 subjects experienced a Profound or Total loss of hearing sensitivity by 6-months. All 15 subjects completed the SSQ, DUQ and MBQ questionnaires preoperatively as well as postoperatively at 6-month evaluation. Results for the Profound and Total hearing loss subgroup are reported below by Self-Assessment Questionnaire.

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[68] Note that for subjects [redacted] the Hybrid Mode was not tested at 6 months as the best unilateral listening mode because the subjects experienced profound or total loss of hearing and did not derive benefit from the Acoustic Component of the Hybrid device. Thus, preoperative Acoustic Alone scores were compared with the postoperative Hybrid Mode as the best unilateral listening condition.

[69] [redacted] did not have a score available for the Combined Mode; results not saved due a software error.

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

As detailed above, the Speech, Spatial, and Qualities of Speech Questionnaire (SSQ) was used as a subject self-assessment of hearing in everyday life across three categories (speech hearing rating scale, spatial rating scale, and sound qualities rating scale). All 15 subjects with profound or total hearing loss completed the SSQ preoperatively and postoperatively at 6-months postactivation. Results are reported below for each scale separately. Individual data are tabled in Appendices 61 and 62, Tab 21. A total score for the SSQ at each test interval was also reported, that reflected averaged scores over the 3 subscales. Table 26 provides a summary of the statistical outcomes, which showed that there were no significant changes in SSQ ratings pre- to postoperatively for the subjects with profound or total loss of hearing. Statistical outputs are provided in Appendix 63, Tab 21.

5.9.7.3.1.1 Speech Hearing Scale

- Preoperative SSQ scores obtained in the Bilateral Acoustic condition for the Profound and Total loss of hearing subgroup ranged from 1.90 to 6.20, with a mean score of 3.73 (N=15).
- At the 6-month evaluation in the Combined Mode scores for the Profound and Total loss of hearing sub group ranged from 0.70 to 7.60, with a mean score of 4.60 (N=15).

Individual comparisons of the preoperative to 6-month postactivation results on the Speech Hearing Scale showed that 9 (60%) of the 15 subjects perceived benefit. Six subjects (40%) indicated a decrement in pre- to postoperative scores.

Table 26: Pre- to postoperative statistical outcomes for the SSQ – profound & total loss of hearing (N=15).

Pre-to-Post Comparison	Change Score Mean ± S.D. (95% C.I)	t (Paired t-test) or S (Signed-Rank Test)	P-Value*
Speech Hearing	-0.87 ± 1.67 (-1.8, 0.05)	t(15) = -2.02	P = 0.063
Spatial	0.01 ± 1.88 (-1.03, 1.05)	t(15) = 0.01	P = 0.989
Qualities	0.01 ± 1.88 (-1.03, 1.05)	t(15) = 0.01	P = 0.989
Total	-0.40 ± 1.56 (-1.27, 0.46)	t(15) = -1.01	P = 0.332

*Student's t-test p-value; signed-rank p-value if normality assumption failed

5.9.7.3.1.2 Spatial Hearing Scale

- Preoperative SSQ scores obtained in the Bilateral Acoustic condition for the Profound and Total loss of hearing sub group ranged from 2.9 to 9.2, with a mean of 5.67 (N=15), and
- At the 6-month evaluation in the Combined Mode scores for the Profound and Total loss of hearing sub group ranged from 2.8 to 8.1, with a mean of 5.66 (N=15).

Individual comparisons of the preoperative to 6-month postactivation results on the Speech Hearing Scale showed that 7 (46.7%) of the 15 subjects perceived benefit. Eight subjects (53.3%) indicated a decrement in pre- to postoperative scores.

5.9.7.3.1.3 Sound Qualities Scale

- Preoperative SSQ scores obtained in the Bilateral Acoustic condition for the Profound and Total loss of hearing sub group ranged from 2.6 to 8.10, with a mean of 5.35 (N=15), and
- At the 6-month evaluation in the Combined Mode scores for the Profound and Total loss of hearing sub group ranged from 3.4 to 7.4, with a mean of 5.69 (N=15).

Individual comparisons of the preoperative to 6-month postactivation results on the Speech Hearing Scale showed that 9 (60%) of the 15 subjects perceived benefit. Six subjects (40%) indicated a decrement in pre- to postoperative scores.

5.9.7.3.1.4 Total SSQ Score

- Preoperative SSQ scores obtained in the Bilateral Acoustic condition for the Profound and Total loss of hearing sub group ranged from 2.67 to 7.83, with a mean of 4.91 (N=15), and
- At the 6-month evaluation in the Combined Mode scores for the Profound and Total loss of hearing sub group ranged from 2.57 to 7.4, with a mean of 5.32 (N=15).

Individual comparisons of the preoperative to 6-month postactivation results on the Speech Hearing Scale showed that 9 (60%) of the 15 subjects perceived benefit. Six subjects (40%) indicated a decrement in pre- to postoperative scores.

5.9.7.3.2 Device Use Questionnaire (DUQ)

The Device Use Questionnaire (DUQ) was designed as an "in-house" usability metric to determine subjective preferences and satisfaction with regards to device use in various listening environments.

All 15 subjects with profound or total loss of hearing completed the DUQ pre- and postoperatively at 6-months postactivation. Individual data are tabled in Appendices 64

and 65, Tab 21. A brief summary of responses to some of the key questions posed can be found below.

Preoperative Results:

- Many subjects, 66.7% (10/15), reported the use of bilateral hearing aids as the overall preferred way of listening most of the time.
- When asked to indicate how satisfied they were with their performance in their overall preferred way of listening
    - Most subjects, 80% (12/15), reported being 'dissatisfied' or 'very dissatisfied, and
    - Few subjects, 13.3% (2/15), reported being "satisfied" or "very satisfied".

Postoperative Results:

- Table 27 summarizes the responses when subjects (N = 15) were asked to describe their overall preferred way of listening most of the time since receiving the Nucleus Hybrid Cochlear Implant:

Table 27: Preferred way of listening since receiving the Nucleus Hybrid cochlear implant – profound & total loss of hearing.

Condition	6 Months Postactivation
Acoustic only	N/A
Bimodal	80.0% (12/15)
Combined	20.0% (3/15)
Hybrid	N/A

- Eight of 15 subjects (53.3%) reported that it was "very easy" or "moderately easy" to adjust to two different systems (electric and acoustic) at 6 months postactivation whereas only 3 of the 15 subjects (20.0%) reported that it was "moderately difficult" or "very difficult".

- Many subjects, 60.0% (9/15), reported that sound was the most pleasant and natural in the Bimodal Mode at 6 months postactivation whereas 5 of the 15 subjects (33.3%) still preferred the Combined Mode and 1 subject (6.7%) preferred hearing aids.
- Overall ease of listening was reported greatest in the Bimodal Mode, 66.7% (10/15), at 6 months postactivation whereas some subjects (33.3% (5/15) still preferred the Combined Mode.
- Many subjects, (53.3%), reported being "very satisfied" or "satisfied" with their overall performance at 6 months postactivation, whereas some subjects, 40% (6/15), stated they were "dissatisfied".
- Even though some (40%) of the 15 subjects who experienced a profound or total loss of hearing sensitivity were dissatisfied with their overall performance at 6 months postactivation, 53.3% (8/15) reported being "satisfied" or "very satisfied" with the decision they made to receive the Nucleus Hybrid Cochlear Implant at 6 months postactivation. Only 20% of the subjects (3/15) reported being "dissatisfied" and 26.7% (4/15) were neutral regarding their decision to receive the Nucleus Hybrid Cochlear implant at 6 months postactivation.

As shown by the responses summarized above regarding preferred listening mode, sound quality, satisfaction, and adjustment results indicate that the subgroup of subjects who experienced a profound or total loss of hearing sensitivity preferred to use and are satisfied with the Nucleus Hybrid Cochlear Implant.

5.9.7.3.3 Musical Background Questionnaire (MBQ)

The Musical Background Questionnaire (MBQ) examines musical training prior to hearing loss, listening habits with hearing aids, satisfaction with hearing aids for music listening, quality of music with hearing aids, enjoyment of musical styles with hearing aids, enjoyment of different instrumental timbres with hearing aids. All 15 subjects of the Profound and Total hearing loss subgroup completed the MBQ preoperatively and

postoperatively at 6-months postactivation. A summary of the results for each question, for both the data points, can be found in Appendices 66 and 67, Tab 21.

- Preoperative Results
    - Ten of the 15 subjects (66.7%) who experienced a profound or total loss of hearing sensitivity reported their preferred way of listening to music was with bilateral hearing aids whereas 20.0% (3/15) preferred to listen with no hearing aids and the remaining subjects 13.3% (2/15) preferred to listen with their left hearing aid only.
    - With their hearing loss and in the best listening condition, subjects chose to listen to music:
        - 53.3% (8/15) less than 3 hours per week
        - 26.7% (4/15) 3-5 hours per week
        - 6.7% (1/15) 6-8 hours per week
        - 13.3% (2/15) 9 or more hours per week
    - With their hearing loss and in the best listening condition:
        - 0% (0/15) avoid music
        - 0% (0/15) never really listen to music
        - 53.3% (8/15) listen, but find music difficult to understand
        - 13.3% (2/15) listen, but find music unimportant
        - 26.7% (4/15) find music very enjoyable
        - 6.7% (1/15) listen, and find music important
- Postoperative Results
    - Subjects preferred to listen to music in the following conditions:
        - 73.3% (11/15) in the Bimodal Mode
        - 20.0% (3/15) in the Combined Mode
        - 6.7 % (1/15) in the left hearing aid only condition with no cochlear implant

- When asked how often subjects chose to listen to music before their implant, they reported:
  - 0% (0/15), never
  - 60.0% (9/15), less than 3 hours per week
  - 13.3% (2/15), 3-5 hours per week
  - 13.3% (2/15), 6-8 hours per week
  - 13.3% (2/15), 9 or more hours per week
- When asked how often they choose to listen to music after their implant in their best listening condition:
  - 0% (0/15), never
  - 53.3% (8/15), less than 3 hours per week
  - 33.3.% (5/15), 3-5 hours per week
  - 6.7% (1/15), 6-8 hours per week
  - 6.7% (1/15), 9 or more hours per week
  - Subjects were asked to indicate how music sounds currently with respect to different rating scales. Average ratings are summarized below in Table 28.

As shown by the responses summarized above for the SSQ, DUQ and MBQ, most of the individuals who experienced a profound or total loss of hearing sensitivity used the Bimodal Mode (80%) as their preferred listening condition. The subgroup demonstrated similar patterns of listening to music before and after cochlear implantation with the Nucleus Hybrid L24 Implant System. Forty percent (6) of the 15 subjects who experienced a profound or total loss of hearing sensitivity were dissatisfied with their overall performance at 6 months postactivation, however 53.3% (8/15) reported being "satisfied" or "very satisfied" with the decision they made to receive the Nucleus Hybrid Cochlear Implant at 6 months postactivation. Two of the subjects ([redacted] and [redacted] who reported being dissatisfied with performance were reimplanted after the 12-

month postactivation evaluation was completed (see cases summaries under 5.9.8.2.2.12 Reimplantation after Profound or Total Loss of Low-Frequency Hearing).

Table 28: Average ratings for music qualities.

Question (rating from 0 to 10)	Average Preoperative Rating (N=50)	Average Postoperative Rating (N=48)
0 - Empty to 10 - Full	**5.3**	**5.8**
0 – Unpleasant to 10 - Pleasant	**5.8**	**5.5**
0 - Unnatural to 10 – Natural	**5.3**	**5.4**
0 - Clear to 10 Fuzzy	5.4	5.2
0 – Sounds like Music 10 – Does not	4.3	5.1
0 – Complex to 10 - Simple	4.2	5.1
0 – Easy to Follow to 10 - Difficult	5.7	5.2
0 – Like sound of music very much to 10 - Dislike	3.3	4.0

5.9.8 Safety Results

5.9.8.1 Unanticipated Adverse Events

As of May 31, 2013, there have been no unanticipated device effects reported for this study.

5.9.8.2 Anticipated Adverse Events

Anticipated adverse events reported to date for this study are tabulated in Appendix 68, Tab 22. These adverse events are consistent in character and severity to those reported for other cochlear implant devices. For comparison, Appendix 69, Tab 22 provides a

tabulation of the events observed during the Freedom (the same device platform as the Hybrid L24) clinical trial (P970051/S028).

This study involved implanting subjects with residual low-frequency hearing sensitivity. For the purposes of adverse event reporting, any change in hearing that resulted in a profound (> 90 dB HL) or total (no measurable hearing) loss of low-frequency hearing (averaged over the range 125 through 1000 Hz) in the implanted ear was considered an anticipated adverse event and included in the adverse event tabulations and analyses. Cases where the Hybrid L24 implant was explanted and replaced with a new device are presented below, under their own section with this report. The four cases [redacted] and [redacted]) related to existing, defined adverse events, namely, profound or total loss of hearing.

Sixty-five adverse events were observed during the study, involving 34 of the 50 subjects. Fifty events were considered medical/surgical in nature and 15 device related. Twenty-two of the 50 medical/surgical events were cases of postoperative profound or total loss of low-frequency hearing. Appendix 70, Tab 22 lists the individual adverse events observed during the course of the study along with the number of events that occurred and the number of subjects involved, in addition to calculations that express the rate (events/10 patient-years) as well as the percentage of subjects involved for each event observed. All events observed occurred at less than 1 event per 10 patient-years, except for profound or total loss of hearing that occurred at a rate consistent with 2.13 events per 10 patient-years.

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 13). The adverse events observed during the study tended to occur within the first 6 to 8 months of device use post-surgery.

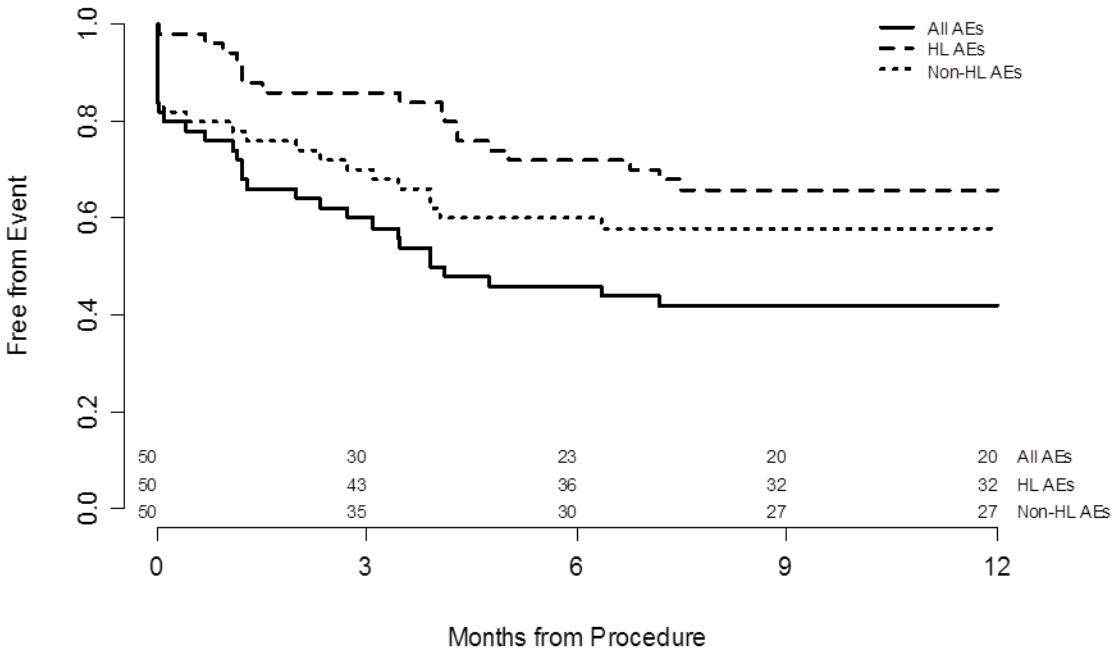

Figure 13: Kaplan-Meier curves showing freedom from all adverse events (solid line), non-hearing related adverse events (dotted line), and profound/total loss of hearing (dashed line).

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 and for profound/total loss of hearing), the results of which are provided in Appendix 70, Tab 22. 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).

The following sections provide individual case summaries under headings corresponding to each adverse event type observed during the study. The 43 non-hearing related adverse events summarized below were not considered serious in nature, and as of this report all

had resolved. Adverse events related to changes in hearing that resulted in profound or total loss of low-frequency hearing (N=22) were considered 'Closed, Not Resolved.'

5.9.8.2.1 Device Related

5.9.8.2.1.1 Open-Circuited Electrodes

Open-circuit electrodes were reported for 6 subjects, all of which involved only one electrode in the array. All were resolved by excluding the affected electrode from the subject's processor program (MAP). Two subjects had a short-circuited electrode pair, 1 subject had a partially shorted electrode pair, and 1 subject had both a short-circuited electrode pair and an open-circuit electrode. All cases were resolved by exclusion of the affected electrodes from the subjects' processor programs. In the latter case ([redacted] impedance testing indicated the affected electrodes were no longer shorted and were reintroduced into the subject's MAP at the 3-month evaluation. A final, 11th, case [redacted]) had a device with a fault mode that resulted in all active electrodes being partially shorted together. This device was surgically replaced with a Nucleus 5 cochlear implant (see case summary for [redacted] under 5.9.8.2.2.12 Reimplantation after Profound or Total Loss of Low-Frequency Hearing).

Subject [redacted]

Surgery Date: May 6, 2010

Date of Occurrence: May 6, 2010

Issue: Open-Circuit Electrode

Status: Resolved

An open circuit was reported for this subject intraoperatively on electrode 13. The issue was resolved through programming; the electrode was not included in the subject's processor program (MAP) at device activation, June 3, 2010.

Subject [redacted]

Surgery Date: February 26, 2011

Date of Occurrence: February 26, 2011

Issue: Open-Circuit Electrode

Status: Resolved

An open circuit was reported for this subject intraoperatively on electrode 20. The issue was resolved through programming; the electrode was not included in the subject's processor program (MAP) at device activation, March 22, 2011.

Subject [redacted]

Surgery Date: November 20, 2008

Date of Occurrence: November 20, 2008

Issue: Open-Circuit Electrode

Status: Resolved

Electrode 22 was reported to be open circuited at the initial activation, December 22, 2008, and resolved by exclusion from the processor program (MAP).

Subject [redacted]

Surgery Date: August 26, 2008

Date of Occurrence: August 26, 2008

Issue: Open-Circuit Electrode

Status: Resolved

An open circuit was reported for this subject intraoperatively on electrode 13. The issue was resolved through programming; the electrode was not included in the subject's processor program (MAP) at device activation, September 25, 2008.

Subject [redacted]

Surgery Date: March 17, 2010

Date of Occurrence: April 19, 2010

Issue: Open-Circuited Electrode

Status: Resolved

An open circuit was reported at initial activation, April 19, 2011, on electrode 12 for subject [redacted], which was resolved through programming. The open circuit was not noted during intraoperative testing March 17, 2011.

Subject [redacted]

Surgery Date: March 30, 2011

Date of Occurrence: October 26, 2012

Issue: Open-Circuited Electrode

Status: Resolved

During a follow-up visit, October 26, 2012, it was noted that electrode 1 was open-circuited based on impedance measures made during routine reprogramming. The subject's clinician reported that the subject had not noticed any difference in sound quality. However, electrode 1 was disabled in the subject's sound processor MAP.

5.9.8.2.1.2 Short-Circuited Electrodes

Subject [redacted]

Surgery Date: May 9, 2011

Date of Occurrence: May 9, 2011

Issue: Short-Circuited Electrodes

Status: Resolved

Intraoperatively, it was noted that electrodes 18 and 19 were shorted to each other. The issue was resolved at the initial activation of the device by programming the electrodes out of the subject's processor MAP at device activation, June 9, 2011.

Subject [redacted]

Surgery Date: June 15, 2011

Date of Occurrence: October 12, 2011

Issue: Short-Circuited Electrodes

Status: Resolved

Electrodes 17 and 18 were reported as short-circuited 3 months postactivation, October 12, 2011, for subject [redacted] This issue was resolved through programming.

5.9.8.2.1.3 Short- and Open-Circuited Electrodes

Subject [redacted]

Surgery Date: January 12, 2011

Date of Occurrence: January 12, 2011

Issue: Short- and Open-Circuited Electrodes

Status: Resolved

Electrodes 11 and 13 were recorded as short-circuited to each other and electrode 22 as open-circuited in the intraoperative (January 12, 2011) and initial activation (February 10, 2011) impedance reports. This was resolved by not including these electrodes in the subject's processor program. At the 3-month evaluation the impedances for electrodes 11 and 13 were normal and introduced into the subject's processor program (MAP).

5.9.8.2.1.4 Partial Short-Circuited Electrodes

Subject [redacted]

Surgery Date: April 18, 2011

Date of Occurrence: April 18, 2011

Issue: Partial Short-Circuit Electrodes

Status: Resolved

A likely partial short-circuit between electrodes was noted for this subject at the programming follow-up evaluation, July 21, 2011, between electrodes 17 and 18. A review of this subject's impedance history revealed that the impedances for these electrodes were considerably lower than those measured on other electrodes. This was evident in measures made at and since the device was surgically placed on April 18, 2011. The issue was resolved through programming by excluding the affected electrodes from the subject's processor program (MAP).

Subject [redacted]

Surgery Date: January 5, 2011

Date of Occurrence: May 18, 2011

Issue: Partial Short-Circuited Electrodes

Status: Resolved

Concerned about the subject's limited progress, an integrity test (a test done to determine whether the implant is working according to manufacturer specifications) was performed at the request of the clinician, May 18, 2011. Together with impedance test results, the integrity test was consistent with partial shorting of electrodes 5 through 22 and no malfunction of the receiver/stimulator. Based on the result of the impedance and integrity tests, coupled with limited benefit with the device, the patient elected to be explanted and reimplanted with a Nucleus 5 cochlear implant. The patient was reimplanted on June 29, 2011 with the Nucleus 5 implant and reportedly there were no complications. An email from the subject's clinician indicated that the subject scored 32% for the CNC word test 2

weeks after activation of the Nucleus 5 device and 52% 1 month after device activation. These scores compare favorably with the subjects preoperative score of 27% with a hearing aid in the ear-to-be implanted. The subject at this point doesn't feel that comprehension is where it should be although the clinician believes the subject is doing very well with the Nucleus 5 cochlear implant. The subject's 1-month sentence recognition in quiet as measured using HINT sentences was 77% and not quite where the subject was preoperatively, though improved over the 2-week score of 52%. The subject's clinician theorized that the subject's impression is a reflection of the HINT performance but believed that the subject was making progress. The subject was seen by the site audiologist on August 30, 2011, when HINT and CNC scores were reported to be unchanged. The subject was reported to be feeling better about the performance with the Nucleus 5 device (see summary under 5.9.8.2.2.12 Reimplantation after Profound or Total Loss of Low-Frequency Hearing).

5.9.8.2.1.5 Sound Quality Issue

Two subjects reported sound quality issues with the Hybrid sound processor, one of which resolved and one of which was closed, not resolved.

Subject [redacted]

Surgery Date: January 28, 2010

Date of Occurrence: May 13, 2010

Issue: Sound Quality

Status: Resolved

Subject [redacted] reported hearing a "chirping" sound with device on just prior to the 3-month evaluation, May 13, 2011, when the subject experienced a change in acoustic low-frequency hearing of > 30 dB (described under 5.9.8.2.2.11 Profound or Total Loss of Low-Frequency (125 through 1000 Hz) Hearing below). It was not clear if this was associated with the change in hearing, but no further issues with sound quality were

reported at the 3-month evaluation, June 17, 2010, and none have been reported since, even at the most recent 12-month evaluation that occurred March 23, 2011. An email from the subject's clinician, dated August 30, 2011 confirmed that the chirping sound had resolved (gone away).

Subject [redacted]

Surgery Date: May 9, 2011

Date of Occurrence: June 9, 2011

Issue: Sound Quality

Status: Closed, Not Resolved

Subject [redacted] reported a problem with sound quality to the study site, June 13, 2011, noting a static-like sound in the presence of speech, at the device programming follow-up June 20, 2011. The sound was evident in the electric pathway only. It is not unusual for subjects to report static or high-pitched sounds when first activated, presumably related to an accommodation period to the new high-frequency stimulation provided by the cochlear implant. However, new sound processors (Hybrid and conventional Freedom devices) were fitted but the sound persisted with both processor types, consistent with the static being non-hardware related. Following the subject's most recent 12-month evaluation, June 12, 2012, the subject's audiologist reported in an email communication that, while the subject continues to use the Hybrid system and derives benefit, the static sound persists. The subject has adapted to the presence of the sound but expressed that it would gratifying if the sound could be eliminated.

On November 7, 2012 extensive troubleshooting and programming support was provided by the Sponsor, including the programming of non-Hybrid sound processors (Freedom and Nucleus 5). The subject continued to report the presence of static with electric stimulation regardless of the type of sound processor. Reprogramming was completed but

nothing resolved the complaint of static. A static/buzz test was completed in conjunction with integrity testing with no evidence of receiver/stimulator malfunction.

At a follow-up session, December 4, 2012, several programming changes were made including changing the frequency allocation table and 250 Hz MAP. None of the programming changes alleviated the complaint of static in the electric condition. Speech perception testing was completed during the appointment (electric only condition) with the following results: HINT (quiet) 41%, AzBio (quiet) 36%, AzBio (noise +5) 0%, CNC (quiet) 42%. The scores observed are consistent speech perception scores obtained as part of the study (e.g., 12-month CNC score was 48% in the Hybrid mode, compared with 15% preoperatively with a hearing aid). [redacted] had asymmetrical speech perception scores preoperatively and had a scan to rule out the presence of a tumor. The subject's audiologist reported that no tumor was found at the time. Assessment for central pathology given the history of asymmetry and current complaint with sound quality was discussed but left to the subject's clinicians to pursue if determined necessary. There were no further programming recommendations.

5.9.8.2.2 Medical/Surgical

5.9.8.2.2.1 Increased Tinnitus or Postoperative Tinnitus not Present Preoperatively

Information concerning the presence of tinnitus was solicited as part of the preoperative candidacy evaluation and the adverse event reporting process. Subjects were asked questions, by the investigator, related to the presence of tinnitus unilaterally or bilaterally, its nature (continuous or intermittent), whether or not it was present previously, and whether or not it the tinnitus had increased in intensity and/or frequency. What follows immediately below are case summaries for those subjects who reported the presence of tinnitus that had increased in intensity and/or frequency or was present postoperatively and not reported preoperatively.

Thirteen subjects reported 14 instances of increased tinnitus or tinnitus not present preoperatively.

- Seven [redacted] of these 13 individuals reported the presence of tinnitus in the implanted ear preoperatively.
- [redacted] reported increased tinnitus on two occasions and both instances were considered separate events. One instance was associated with a change in low-frequency hearing sensitivity and summarize separately under 5.9.8.2.2.11 Profound or Total Loss of Low-Frequency (125 through 1000 Hz) Hearing.

All 14 cases (across the 13 subjects) were considered 'Resolved' (tinnitus absent or improved to a prior state) at the time of this report. None of the cases reported below warranted medical treatment beyond observational monitoring. Note that cases ([redacted] and [redacted] where tinnitus was reported as a symptom concomitant with changes in hearing sensitivity are summarized separately, under 5.9.8.2.2.11 Profound or Total Loss of Low-Frequency (125 through 1000 Hz) Hearing. However, such instances were treated as separate events for adverse event tabulation.

5.9.8.2.2.2 Increased Tinnitus

Subject [redacted]

Surgery Date: August 13, 2009

Date of Occurrence: November 4, 2009

Date Reported: November 4, 2009

Issue: Increased Tinnitus

Status: Resolved

Preoperatively, [redacted] reported minimal intermittent tinnitus in the left, unimplanted ear, noticeable when not using a hearing aid. Postoperatively, the subject reported increased intermittent tinnitus bilaterally at device activation, September 18, 2009. No treatment course was indicated. By 3 months postactivation (December 21, 2009), the subject continued to report bilateral intermittent tinnitus but did not consider the tinnitus as increased in intensity and/or frequency. At a follow-up evaluation, March 17, 2010, the subject reported the tinnitus as intermittent in both ears, not increased and minimal in level, consistent with the level reported preoperatively.

Subject [redacted]

Surgery Date: May 21, 2010

Date of Occurrence: June 7, 2011

Date Reported: June 7, 2011

Issue: Increased Tinnitus

Status: Resolved

Subject [redacted] reported an increase in bilateral (intermittent in nature) tinnitus at the 12-month evaluation on June 7, 2011. This subject reported continuous bilateral tinnitus preoperatively and consistently throughout the postoperative period. No treatment course was indicated. An email communication from the subject via the site clinician, September 6, 2011, indicated that the tinnitus was no longer increased and was reduced compared with the preoperative status for the implanted ear. At a follow up evaluation, December 21, 2011, the subject again reported tinnitus, this time continuous and increased in nature. More recently, May 2, 2013, [redacted] confirmed by email via the subject's clinician that the tinnitus was resolved (not increased over prior level). In fact, the subject reported believing that the tinnitus was improved since receiving the implant.

Subject [redacted]

Surgery Date: July 9, 2010

Date of Occurrence: February 27, 2012

Date Reported: February 27, 2012

Issue: Increased Tinnitus

Status: Resolved

Preoperatively, [redacted] reported intermittent tinnitus bilaterally and continued to report the presence of tinnitus throughout the postoperative period. At a follow-up visit, February 27, 2012 the subject reported an increase in the tinnitus. However, during a more recent visit December 17, 2012 the tinnitus was no longer reported to be increased in intensity and/or frequency.

Subject[redacted]

Surgery Date: June 20, 2011

Date of Occurrence: June 20, 2011

Date Reported: June 20, 2011

Issue: Increased Tinnitus

Status: Resolved

[redacted] reported continuous bilateral tinnitus preoperatively. An increase in tinnitus was reported immediately following surgery on June 20, 2011 and characterized as intermittent bilaterally. By device activation, July 19, 2011, the tinnitus was reported as present bilaterally and intermittent but not increased in intensity and/or frequency. Email communication, September 1, 2011, via the subject's clinician indicated that the subject considered that the tinnitus had always been intermittent and happened often prior to surgery, sometimes lasting for days, sometimes for a few hours. After surgery the subject believed it was worse being more intense and more frequent. Once through the healing period the subject reported that the tinnitus was occurring less often but wasn't sure if the intensity was any different as the tinnitus had not returned for some time. At the 6-month

postactivation, January 18, 2012, evaluation the subject reported there to be no tinnitus present. At a follow up visit, January 8, 2013, the subject reported continuous bilateral tinnitus but not increased in intensity and/or frequency.

Subject [redacted]

Surgery Date: March 17, 2010

Date of Occurrence: April 19, 2010

Date Reported: April 19, 2010

Issue: Increased Tinnitus

Status: Resolved

At initial activation, April 19, 2010, it was reported that the subject experienced increased tinnitus and perceived a decrease in hearing sensitivity. With use of the Hybrid implant a *decrease* in tinnitus was noted. Audiometric testing at that time indicated that low-frequency was 11 dB poorer than preoperative levels, not consistent with any significant change in hearing sensitivity. At the most recent 12-month evaluation, on April 13, 2011, the subject's average low-frequency hearing (over 125 through 1000 Hz) was within 10 dB of preoperative levels. At the programming follow up, May 26, 2010, the tinnitus was noted to have improved and at no time postoperatively did the subject answer in the affirmative to the question: "Has the tinnitus increased in intensity and/or frequency?" Email communication on August 31, 2011, from the subject's clinician, confirmed that the tinnitus had improved to a level no worse than that observed preoperatively.

Subject [redacted]

Surgery Date: February 18, 2011

Date of Occurrence: June 5, 2011

Date Reported: July 14, 2011

Issue: Increased Tinnitus

Status: Resolved

Subject [redacted] reported relatively mild continuous tinnitus in the right ear prior to implantation in that ear. At the 3-month evaluation, July 14, 2011, the subject reported a 3-week period in which an increase in tinnitus was noticed in the implanted ear, upon device removal, at night. By morning, the tinnitus was reported to be gone. This corresponded to a time when the subject was taking medication to relieve pain associated with a broken leg. By the 3-month evaluation, the subject reported no tinnitus unless all hearing devices were removed. When in a quiet environment, the subject reported minimal tinnitus. At 6 and 12 months postactivation the subject reported the presence of intermittent tinnitus in the implanted ear but not increased over that experienced preoperatively. At a follow-up visit, April 3, 2013, the subject reported no tinnitus to be present.

5.9.8.2.2.3 Postoperative Tinnitus Not Present Preoperatively

Subject [redacted]

Surgery Date: May 6, 2010

Date of Occurrence: May 6, 2010

Date Reported: May 6, 2010

Issue: Tinnitus not present preoperatively

Status: Resolved

Preoperatively, [redacted] reported continuous tinnitus in the left, unimplanted ear. Postoperatively, the subject reported continuous tinnitus bilaterally at the intraoperative evaluation (May 6, 2010) and at device activation, June 3, 2010 but not increased over prior levels. No treatment course was indicated by the site. The subject continued to report bilateral, continuous or intermittent, tinnitus but did not consider the tinnitus as increased in frequency or level.

Subject [redacted]

Surgery Date: July 28, 2010

Date of Occurrence: September 1, 2011

Date Reported: September 1, 2011

Issue: Tinnitus not present preoperatively

Status: Resolved

Subject [redacted] reported the presence of intermittent pulsatile tinnitus at the 12-month evaluation, September 1, 2011, in the implanted ear. No treatment course was indicated by the study site and further information as the subject's status was requested of the site by email July 27, 2012. The subject had subsequently been scheduled for follow-up visits to the clinic but had canceled or not shown for appointments. Follow-up was obtained via email communication, April 25, 2013 and subject [redacted] indicated that the tinnitus (attributed to hearing the heart beat) had resolved.

Subject [redacted]

Surgery Date: February 26, 2011

Date of Occurrence: September 20, 2011

Date Reported: September 20, 2011

Issue: Tinnitus not present preoperatively

Status: Resolved

Subject [redacted] reported the presence of minimal intermittent tinnitus at the 6-month evaluation, September 20, 2011, bilaterally. No treatment course was indicated by the study site. However, at a follow-up visit October 10, 2012 no tinnitus was reported to be present.

Subject [redacted]

Surgery Date: October 25, 2010

Date of Occurrence: January 10, 2012

Date Reported: January 10, 2012

Issue: Tinnitus not present preoperatively

Status: Resolved

Subject [redacted] reported the presence of intermittent tinnitus at the 12-month evaluation, January 10, 2012, bilaterally. No treatment course was indicated by the study site. However, at a follow-up visit December 19, 2012 no tinnitus was reported to be present.

Subject [redacted]

Surgery Date: July 8, 2009

Date of Occurrence: August 17, 2010

Date Reported: August 17, 2010

Issue: Tinnitus not present preoperatively

Status: Resolved

[redacted] reported tinnitus in the left, implanted ear at the 12-month evaluation, August 17, 2010, which had not previously been reported, preoperatively or postoperatively. A report dated November 4, 2010 indicated that the tinnitus was absent. More recently, March 21, 2013 the subject reported the presence of tinnitus in the left, implanted ear but was not reported to be increased in level and/or frequency.

Subject [redacted]

Surgery Date: January 12, 2011

Date of Occurrence: February 10, 2011

Date Reported: February 10, 2011

Issue: Tinnitus not present preoperatively

Status: Resolved

[redacted] reported tinnitus at initial activation, February 10, 2011, in the implanted ear which had not previously been reported. However, since that time the subject has reported the absence of tinnitus through the most recent evaluation on March 15, 2013.

5.9.8.2.2.4 Dizziness or Imbalance

Symptoms of dizziness or imbalance were reported for 7 subjects, all of which had resolved as of this report. Note that cases [redacted] where symptoms were reported concomitant with changes in hearing sensitivity were summarized separately under 5.9.8.2.2.11 Profound or Total Loss of Low-Frequency (125 through 1000 Hz) Hearing.

Subject [redacted]

Surgery Date: July 9, 2010

Date of Occurrence: November 30, 2011

Date Reported: December 10, 2011

Issue: Dizziness

Status: Resolved

[redacted] reported dizziness related to a possible viral illness November 30, 2011, unrelated to the device, per the subject's physician. Prednisone was prescribed November 11, 2011 at 20 mg twice per day for 7 days, and continued by the subject's primary care physician through November 29, 2011to treat the viral illness. At a follow-up visit, December 17, 2012, the dizziness was reported as resolved after physical therapy.

Subject [redacted]

Surgery Date: August 19, 2011

Date of Occurrence: August 19, 2011

Date Reported: September 20, 2011

Issue: Dizziness

Status: Resolved

[redacted] reported slight dizziness following surgery that resolved on its own completely 3 to 4 days postoperatively.

Subject [redacted]

Surgery Date: June 20, 2011

Date of Occurrence: June 20, 2011

Date Reported: June 22, 2011

Issue: Dizziness

Status: Resolved

[redacted] reported dizziness after surgery that lasted 9 days. At the initial activation of the device, July 19, 2011, the site reported that the dizziness was resolved.

Subject [redacted]

Surgery Date: September 27, 2011

Date of Occurrence: January 28, 2012

Date Reported: January 30, 2012

Issue: Imbalance

Status: Resolved

[redacted] reported mild imbalance at the 3-month evaluation, January 30, 2012 that had resolved with time and with physical activity.

5.9.8.2.2.5 Vertigo

Vertigo was reported in two cases, both of which had resolved as of this report. Note that for subject [redacted] vertiginous symptoms were reported concomitant with a change in hearing sensitivity and summarized separately under 5.9.8.2.2.12 Reimplantation after Profound or Total Loss of Low-Frequency Hearing.

Subject [redacted]

Surgery Date: January 6, 2011

Date of Occurrence: July 18, 2011

Date Reported: September 12, 2011

Issue: Vertigo

Status: Resolved

[redacted] reported vertiginous episodes on July 18 and August 3, 2011 (between 3 and 6 months postactivation). These episodes lasted 36 to 48 hours and resolved on their own. The subjects reported a third episode occurred September 10, 2011. The subject's physician prescribed Niacin 50 mg TID (3 times per day) and Meclizine 25 mg TID for 3 days. The subject was reported (by phone) to be almost asymptomatic 24 hours after the medication was administered. More recently, it was reported that the subject continues to have vertiginous episodes and had another episode December 8, 2011. The subject reported the event occurred at night and took Meclizine as prescribed by the cochlear implant surgeon for 11 days (with tapering). The subject also consults with her own physician who has provided a standing prescription (60 mg of Prednisone for 6 days, then 40 mg for 1 day, 20 for 1 day, 10 for 1 day, 5 for 1 day and then off) to be administered by the subject when experiencing symptoms. The subject's primary physician believes that the subject has vestibular migraines. Email communication between the cochlear implant audiologist and the subject's own physician February 2, 2012, indicates that the subject has a history of migraines and was medicated (Nortiriptyline) for this prior to

cochlear implantation. The physician is not convinced that these vertiginous episodes are related to the implant and that symptoms fit a diagnosis of recurrent vestibular neuritis. Since the subject presented with a 100% weakness in the implanted (left) ear prior to surgery September 12, 2011, the physician could not be sure if the vestibular issues are associated with that ear or not. The physician indicated that Videonystagmography may be repeated to establish that the contralateral ear is not involved. More recently, February 9, 2012, the subject's audiologist reported that [redacted] is participating in vestibular rehabilitation, which is making a big difference. An email communication, January 3, 2012, with the subject's audiologist indicated that vestibular symptoms had resolved.

5.9.8.2.2.6 Decrease in Performance

Subject [redacted]

Surgery Date: September 27, 2011

Date of Occurrence: May 10, 2012

Date Reported: May 10, 2011

Issue: Decrease in Performance

Status: Closed, Not Resolved

On May 11, 2012 the Sponsor received a phone call from the subject's audiologist in response to an observed decrease in performance at the 6-month postactivation visit, on May 10, 2012, compared with that observed at the 3-month evaluation on January 31, 2012 (also see case summary for [redacted] under 5.9.8.2.2.11 Profound or Total Loss of Low-Frequency (125 through 1000 Hz) Hearing). A review of the subject's impedances indicated increased impedances on electrodes 17 through 22, primarily on electrodes 17, 18 and 19 relative to prior measures. Comfort level requirements appeared to be relatively stable with decreased threshold levels. The subject's audiologist reported that threshold levels were reduced to address a quality issue, so they did not represent lowered measured threshold levels. [redacted] reported a hissing sound and globally

lowering the T levels by 6 units helped with this. The subject had always reported a high-pitched percept, that on May 10, 2012 was reported as "distorted tinniness", suggestive a change in sound quality. The subject reported sound delivered to more basal electrodes, from electrode 13 up to be distorted. Electrode11 was particularly so and was removed from the device MAP. However, the most significant observation was that performance via the device appeared to be reduced compared with the prior 3-month evaluation.

The subject reported an episode where the sound via the processor was suddenly loud and the subject reduced the volume in the meantime. On May 10, 2012 the subject preferred the use of a higher volume setting. The subject reported no tinnitus, no change in contralateral hearing was noted, no changes in medical condition or medications, except that subject did experience a fall recently and was on pain medication. Of note is that the subject's spouse had passed away recently.

The subject's audiologist requested an integrity test, which was completed May 15, 2012 with no evidence of device malfunction found. Following the integrity test and further program adjustments, performance testing was completed and US08 correctly identified 44% of CNC words and 62% phonemes, and improvement over that measured on May 10, 2012.

[redacted] was evaluated at 12 months postactivation, November 20, 2012. No programming issues were reported at this time. Performance measures were similar to those measured at the 6-month evaluation. Subject [redacted] scored 16% for the CNC word test in the cochlear implant alone mode compared with 59% using a hearing aid in the implanted ear, preoperatively. In the Bimodal Mode the subject scored 80% compared with 27% preoperatively using the Bilateral Acoustic mode. Speech understanding in noise, as measured using the AzBio sentence test, was 13.1% preoperatively with a hearing aid in the ear-to-be implanted and 15.6% in the cochlear implant alone mode at the 12-month postactivation evaluation. When using the Hybrid cochlear implant in the

Bimodal Mode, the subject scored 88.1% compared with 20.4%, preoperatively, with the Bilateral Acoustic mode.

5.9.8.2.2.7 Skin Irritation due to Externals

Subject [redacted]

Surgery Date: June 22, 2011

Date of Occurrence: September 1, 2011

Date Reported: September 28, 2011

Issue: Skin irritation due to externals

Status: Resolved

On September 28, 2011 (between programming follow-up and 3 months postactivation) the [redacted] was observed to have a small sore in the ear canal. The subject reported that the acoustic component appeared to be too tight and a history of similar issues with hearing aids in the past. New impressions were taken and a new acoustic component provided. At the 3-month postactivation interval, November 4, 2011 the sore ear canal was reported to have resolved after the new acoustic component was fitted.

Subject [redacted]

Surgery Date: March 17, 2010

Date of Occurrence: March 15, 2012

Date Reported: May 15, 2012

Issue: Skin irritation due to externals

Status: Resolved

Subject [redacted] reported that a sore on top of right (implanted) ear that would not go away, during an unscheduled visit to the clinic May 15, 2012. The subject reported using

Mupirocin ointment twice per for a week and then started wearing moleskin directly on the ear. [redacted] reported that the issue had resolved by May 3, 2012.

5.9.8.2.2.8 *Pain in Implant Ear*

Subject [redacted]

Surgery Date: June 3, 2010

Date of Occurrence: September 29, 2012

Date Reported: September 29, 2012

Issue: Pain in implant ear

Status: Resolved

One of the Sponsor's field support staff received a call September 29, 2012 from the subject's audiologist. The audiologist had reportedly received a phone call from the subject's physician requesting assistance. [redacted] was reporting a shocking sensation with and without the processor on the head. The subject also noted decreased hearing but confirmed that he has just stopped using his hearing aid. Although the concern expressed by the physician was initially that it was device related it was subsequently determined that the subject had middle-ear effusion and the shocking sensation was attributable to pain associated with the presence of the effusion.

5.9.8.2.2.9 *Stitch Infection*

Subject [redacted]

Surgery Date: July 8, 2009

Date of Occurrence: July 21, 2009

Date Reported: July 21, 2009

Issue: Local Stitch Infection

Status: Resolved

Subject [redacted] developed a local stitch infection following surgery (July 8, 2009). Oral antibiotics (250 mg of Keflex every 6 hours for 10 days) were prescribed and the infection was resolved by August 3, 2009.

5.9.8.2.2.10 Overstimulation

Subject [redacted]

Surgery Date: January 5, 2011

Date of Occurrence: March 7, 2011

Date Reported: March 7, 2011

Issue: Overstimulation

Status: Resolved

The subject reported a very loud sound while using their secondary sound processor on March 7, 2011; the same program using the primary sound processor was fine. The secondary sound processor was replaced and the issue resolved.

5.9.8.2.2.11 Profound or Total Loss of Low-Frequency (125 through 1000 Hz) Hearing

Over the entire study period (not just the endpoint of 6 months), 22 of 50 subjects experienced changes in low-frequency (LF) hearing, averaged over the range of 125 through 1000 Hz (PTA), resulting in profound or total loss of hearing (LF PTA > 90 dB HL), at a minimum of one test interval. Instances of profound or total loss of hearing were considered 'Closed, Not Resolved,' unless there was evidence of sustained improvement in low-frequency thresholds (over two or more evaluations). One subject, [redacted] demonstrated slightly improved low-frequency hearing by the 12-month postactivation evaluation but was borderline profound (LF PTA = 89 dB HL) and still included in the adverse event analyses. In cases where steroid treatment was initiated dosage information has been included in the individual case summaries below.

Subject [redacted]

Surgery Date: August 13, 2009

Date of Occurrence: December 21, 2009

Issue: Profound/Total Loss of Hearing

Status: Closed, Not Resolved

A change in hearing was first reported for this subject November 2, 2009, 2 months after device activation. The subject was treated with a course of steroids (Prednisone, 60 mg per day for 7 days, with no taper), with no improvement in hearing noted by the 3-month evaluation, December 21, 2009. A low-frequency average decrease in hearing thresholds of 37.4 dB was reported at 3 months postactivation, December 21, 2009, resulting in a profound degree of hearing loss (LF PTA = 99 dB HL). At the 12-month evaluation, September 3, 2010, [redacted] still presented with a profound low-frequency range hearing loss. This subject assessed most recently on November 11, 2011 (2 years postactivation) and low-frequency hearing had remained stable, with a LF PTA of 99.8 dB HL.

Although the subject continued to make use of the acoustic component during the study, it did not appear that acoustic amplification added to the speech perception provided by the cochlear implant alone, based on CNC word recognition. At the 6-month evaluation, [redacted] reported being dissatisfied with performance of the device and neutral in this regard at the 12-month assessment, based on responses to the Device Use Questionnaire (DUQ). However, the subject derived significant benefit using the cochlear implant alone based on speech perception measures. At the 12-month evaluation, the most recent evaluation when speech perception was measured per protocol, [redacted] scored 35% for the CNC word test in Hybrid Mode (34% Cochlear Implant Alone) compared with 9% using Acoustic Alone (Acoustic Alone in the implanted ear), preoperatively. In the Combined Mode, the subject scored 49% (47% Bimodal Mode) compared with 21%

preoperatively using the Bilateral Acoustic mode. Speech understanding in noise, as measured using the AzBio sentence test, was 5.7% preoperatively Acoustic Alone in the ear-to-be implanted and 41% in the Hybrid Mode at the 12-month postactivation evaluation. When using the Hybrid cochlear implant in the Combined Mode the subject scored 45.0% compared with 15.4%, preoperatively, with the Bilateral Acoustic mode.

Subject [redacted]

Surgery Date: July 9, 2010

Date of Occurrence: February 27, 2010

Issue: Profound/Total Loss of Hearing

Status: Closed, Not Resolved

A change in hearing > 30 dB was noted at 500 and 750 Hz during audiometric testing at a postactivation follow up visit September 23, 2010. A 15-to-20 dB air-bone gap was noted and the subject treated with a course of steroids (Prednisone, 20 mg, twice per day for 7 days). By the 6-month evaluation, on January 24, 2011, the condition was noted as improved by the investigator. Audiometric assessment indicated that low-frequency hearing (averaged over 125 to 1000 Hz) was 30 dB poorer than preoperative levels and similar in level to that measured at the 3-month evaluation on November 1, 2010, when it was 27 dB poorer. Tympanometry at the 3 and 6 month evaluations suggested reduced middle ear compliance suggestive of some conductive component. By the 12-month evaluation, on July 18, 2011, low-frequency hearing (averaged over 125 to 1000 Hz) was 26 dB poorer than preoperative levels and therefore considered improved and stable. No significant air bone gap was evident at this evaluation although tympanometry continued to show reduced middle-ear compliance in the implanted ear. Low-frequency hearing loss remained at a moderate to moderate-severe level through 12 months postactivation.

At 18 months postactivation (February 27, 2012), the subject presented with a complete loss of hearing in the implanted ear. A change in hearing was noted by the subject in

November of 2011. In that same time period, the subject presented with dizziness related to a possible viral illness, unrelated to the device, per the subject's physician, that only responded to steroids. Prednisone was prescribed November 11, 2011 at 20 mg twice per day for 7 days, and continued by the subject's primary care physician through November 29, 2011. Although prescribed to alleviate the symptoms related to the viral illness, the subject's physician noted that there was no impact on hearing thresholds. At a follow-up visit, December 17, 2012, the subject continued to present with a total loss of hearing in the implanted ear with no further treatment indicated.

At the 12-month evaluation, the most recent evaluation when speech perception was measured per protocol, [redacted] scored 88% for the CNC word test in Hybrid Mode (57% Cochlear Implant Alone) compared with 48% using Acoustic Alone in the implanted ear, preoperatively. In the Combined Mode, the subject scored 98% (93% Bimodal Mode) compared with 51% preoperatively using the Bilateral Acoustic mode. Speech understanding in noise, as measured using the AzBio sentence test, was 23.5% preoperatively Acoustic Alone in the ear-to-be implanted and 48.1% in the Hybrid Mode at the 12-month postactivation evaluation. When using the Hybrid cochlear implant in the Combined Mode the subject scored 82.4% compared with 28.8%, preoperatively, with the Bilateral Acoustic mode. The subject reported being satisfied with performance (based on DUQ responses) at both the 6- and 12-month evaluations.

Although the subject derived benefit from the device in the Hybrid Mode, [redacted] also demonstrated improved scores in the Cochlear Implant Alone mode, relative to preoperative performance with hearing aids alone. Speech perception scores are not available beyond the 12-month evaluation, per protocol, but the subject reportedly continues to benefit by the use of the Hybrid cochlear implant in the Bimodal Mode.

Subject [redacted]

Surgery Date: July 28, 2010

Date of Occurrence: March 3, 2011

Issue: Profound/Total Loss of Hearing

Status: Closed, Not Resolved

A significant change in hearing was reported at the postactivation follow-up interval, September 23, 2010. At that time, hearing thresholds between 125 and 750 Hz had decreased 30 to 35 dB relative to preoperative levels. A 15 to 20 dB conductive component was evident by audiogram, though tympanometry yielded normal middle-ear mobility. Steroid treatment (Decadron, 8 mg, twice per day for 5 days) was commenced with no improvement in hearing noted. Subject [redacted] showed a low-frequency average decrease in hearing thresholds of 43 dB by 3 months postactivation, which resulted in a severe low-frequency range hearing loss. At 6 months postactivation, March 3, 2011, hearing sensitivity was reported to be worse, such that low-frequency hearing was in the profound range with no evidence of middle-ear involvement. By the most recent 12-month evaluation, September 1, 2011, low-frequency thresholds were on average in the profound range, with the low-frequency decrease corresponding to a decline of 53 dB relative to preoperative levels.

By the 6-month evaluation, [redacted] no longer made use of the acoustic component of the Hybrid sound processor and was assessed at 6 and 12 months using the Cochlear Implant Alone mode and the Bimodal Mode. The subject scored 29% for the CNC word test with Cochlear Implant Alone at 12 months, compared with 46% using Acoustic Alone in the implanted ear, preoperatively. In the Bimodal Mode the subject scored 86% compared with 81% preoperatively using the Bilateral Acoustic mode. Speech understanding in noise, as measured using the AzBio sentence test, was 19.1% preoperatively Acoustic Alone in the ear-to-be implanted and 0% in the cochlear implant (CI) mode at the 12-month postactivation evaluation. However, when using the Hybrid cochlear implant in the Bimodal Mode the subject scored 81.6% compared with 72.2%, preoperatively, with the Bilateral Acoustic mode.

Based on responses to the Device Use Questionnaire at 6 and 12 months postactivation, the subject was dissatisfied with device outcomes. Following the 12-month evaluation, the investigator indicated, anecdotally, that reimplantation was presented as an option to the subject but that [redacted] did not wish to pursue this option. The subject has been working with the clinic's research team on projects designed to improve performance with cochlear implants.

Subject [redacted]

Surgery Date: November 25, 2009

Date of Occurrence: December 17, 2012

Issue: Profound/Total Loss of Hearing

Status: Closed, Not Resolved

Subject [redacted], presented with a low-frequency average decrease in low-frequency hearing thresholds of 22 dB, relative to preoperative levels, 30 months postactivation, July 16, 2012. The subject was reportedly unaware of the change and reported performing "great" with the device. The change in hearing was notable because the subject had demonstrated stable hearing prior to this date. The subject received a Prednisone burst with a taper at 60, 40, 20, 10, and 5 mg for 3 days each. However, the subject's hearing loss progressed by 36 months postactivation, December 17, 2012, resulting in a profound low-frequency hearing loss. No further treatment was prescribed and the subject ceased use of the acoustic component. The sound processor MAP was reprogrammed to deliver broadband electric stimulation to compensate for the loss of low-frequency input in the treated ear.

At the 12-month evaluation, the most recent evaluation when speech perception was measured per protocol, [redacted] scored 88% for the CNC word test in Hybrid Mode (88% Cochlear Implant Alone) compared with 16% using Acoustic Alone in the implanted ear, preoperatively. In the Combined Mode, the subject scored 93% (95%

Bimodal Mode) compared with 41% preoperatively using the Bilateral Acoustic mode. Speech understanding in noise, as measured using the AzBio sentence test, was 21.6% preoperatively Acoustic Alone in the ear-to-be implanted and 72.9% in the Hybrid Mode at the 12-month postactivation evaluation. When using the Hybrid cochlear implant in the Combined Mode the subject scored 54% compared with 25.8%, preoperatively, with the Bilateral Acoustic mode. The subject reported being very satisfied with performance (based on DUQ responses) at both the 6- and 12-month evaluations.

Although the subject derived benefit from the device in the Hybrid Mode, [redacted] also demonstrated improved scores in the Cochlear Implant Alone mode, relative to preoperative performance with hearing aids alone. Speech perception scores are not available beyond the 12-month evaluation, per protocol, but the subject reportedly continues to benefit by the use of the Hybrid cochlear implant in the Bimodal Mode.

Subject [redacted]

Surgery Date: January 21, 2010

Date of Occurrence: June 15, 2010

Issue: Profound/Total Loss of Hearing

Status: Closed but Not resolved

Just prior to the 3-month evaluation, May 20, 2010, subject [redacted], showed a low-frequency decrease in hearing thresholds of 40 to 60 dB. At the 3-month evaluation, June 15, 2010, the average low-frequency change in hearing was 46 dB relative to preoperative levels and at 6 months the loss reported was 41dB, which resulted in a profound low-frequency range hearing loss. This subject does not use the acoustic component of the Hybrid sound processor. Steroid treatment was considered but not initiated due to the uncertainty as to when the loss first occurred. At the more recent, 12-month evaluation completed March 18, 2011; the average change in hearing was 39.2 dB

resulting in low-frequency hearing thresholds of 89 dB HL, just below the threshold for profound loss of hearing (LF PTA > 90 dB HL).

Based on responses to the Device Use Questionnaire at 6 and 12 months postactivation, the subject was very satisfied with device outcomes. At the 12-month evaluation, the most recent evaluation when speech perception is measured per protocol, [redacted] scored 61% for the CNC word test using the cochlear implant alone compared with 33% using Acoustic Alone in the implanted ear, preoperatively. In the Bimodal Mode, the subject scored 95% compared with 69% preoperatively using the Bilateral Acoustic mode. Speech understanding in noise, as measured using the AzBio sentence test, was 8.6% preoperatively Acoustic Alone in the ear-to-be implanted and 64.9% in the CI-alone mode at the 12-month postactivation evaluation. When using the Hybrid cochlear implant in the Bimodal Mode the subject scored 84.2% compared with 46.2%, preoperatively, with the Bilateral Acoustic mode.

Subject [redacted]

Surgery Date: January 6, 2011

Date of Occurrence: August 22, 2011

Issue: Profound/Profound/Total Loss of Hearing

Status: Closed, Not Resolved

One day after surgery, January 7, 2011 the subject's hearing was tested and a decrease in hearing of over 40 dB for air conduction was noted. Bone conduction testing was consistent with preoperative levels at 250Hz. At other frequencies, bone conduction could not be determined due to limitations of the equipment making it difficult to determine if the loss was conductive only. Tympanometry revealed reduced mobility and blood was visualized behind the tympanic membrane. Prednisone at 60 mg was prescribed with a tapered regimen over 10 days (60 mg for 6 days, tapered from day 7 for 4 days). By device activation, February 17, 2011, the subject’s hearing had improved

considerably, such that average low-frequency hearing was only 19 dB poorer than preoperative levels. At the 3-month evaluation, May 10, 2011, hearing thresholds for frequencies from 500 to 1000 Hz were still > 30 dB decreased relative to preoperative levels, but hearing thresholds for 125 and 250 Hz were within 5 to 10 dB of preoperative levels such that the overall decrease in low-frequency hearing was 23.4 dB. By the 6-month evaluation, August 22, 2011, hearing loss had progressed such that the subject had a pre-to-postoperative change in hearing of 64.6 dB, resulting in a profound, almost complete loss of low-frequency hearing. At 12 months, February 9, 2012 the subject presented with a complete loss of low-frequency hearing.

Based on responses to the Device Use Questionnaire at 6 and 12 months postactivation, the subject was satisfied and very satisfied with device outcomes, respectively. At the 12-month evaluation, the most recent evaluation when speech perception is measured per protocol, [redacted] scored 59% for the CNC word test in the cochlear implant alone mode (subject no longer made use of the acoustic component) compared with 12% using Acoustic Alone in the implanted ear, preoperatively. In the Bimodal Mode the subject scored 73% compared with 40% preoperatively using the Bilateral Acoustic mode. Speech understanding in noise, as measured using the AzBio sentence test, was 19.3% preoperatively Acoustic Alone in the ear-to-be implanted and 10.1% in the cochlear implant alone mode at the 6-month postactivation evaluation. When using the Hybrid cochlear implant in the Bimodal Mode the subject scored 60.1% compared with 39.4%, preoperatively, with the Bilateral Acoustic mode.

Subject [redacted]

Surgery Date: February 18, 2011

Date of Occurrence: April 5, 2011

Issue: Profound/Total Loss of Hearing, Increased Tinnitus, Imbalance

Status: Closed, Not Resolved; Increased Tinnitus and Imbalance Resolved

On April 5, 2011, during the programming follow-up evaluation, subject [redacted] reported to the clinic for a hearing assessment following a report of tinnitus and imbalance March 29, 2011. Although [redacted] did not feel that understanding speech was as good as it had been after this time, a decline in hearing sensitivity was not noticed by the subject. Testing April 5, 2011, about 3 weeks after device activation, revealed a change in hearing of more than 30 dB. Tympanometry revealed normal middle-ear compliance. The tinnitus and imbalance was reported to have resolved at this point. Prednisone was prescribed at 60 mg with a tapered regimen over 14 days (60 mg for 10 days, tapered from day 11 for 4 days). Testing at the 3-month postactivation evaluation, July 14, 2011, showed a decline of 41 dB in average low-frequency hearing with a profound degree of hearing loss, similar in level to that measured April 5, 2011. The subject no longer used the acoustic component of the Hybrid sound processor. By the 12-month postactivation evaluation on March 29, 2012 the subject had a profound hearing loss, 51.4 dB poorer than preoperatively. Profound loss of hearing was again confirmed at a more recent follow-up visit, April 3, 2013, 24 months after device activation.

Based on responses to the Device Use Questionnaire at 6 and 12 months postactivation, the subject was satisfied with device outcomes. At the 12-month evaluation, the most recent evaluation when speech perception is measured per protocol, [redacted] scored 42% for the CNC word test with the cochlear implant alone compared with 26% using Acoustic Alone in the implanted ear (Acoustic Alone), preoperatively. In the Bimodal Mode the subject scored 77% compared with 45% preoperatively using the Bilateral Acoustic mode. Speech understanding in noise, as measured using the AzBio sentence test, was 15.8% preoperatively Acoustic Alone in the ear-to-be implanted and 17.5% in the cochlear implant alone mode at the 12-month postactivation evaluation. When using the Hybrid cochlear implant in the Bimodal Mode the subject scored 43.9% compared with 23.2%, preoperatively, with the Bilateral Acoustic mode.

Subject [redacted]

Surgery Date: January 21, 2011

Date of Occurrence: June 1, 2011

Issue: Profound/Total Loss of Hearing, Dizziness

Status: Closed, Not Resolved; Dizziness Resolved

[redacted] reported feeling dizzy and unsteady upon standing, 3 to 4 days following surgery, January 24, 2011. The subject also reported becoming acutely vertiginous on January 27, 2011. Augmentin was prescribed, at 875 mg with 1 tablet twice a day for 10 days, to reduce possible infection that may have contributed to middle-ear hearing loss and/or dizziness. Prednisone at 40 mg with a tapered regimen over 13 days (40 mg for 7 days, tapered from day 8 for 6 days) was also prescribed to address any post-surgical inflammation that may have contributed to the subject's dizziness. On March 28, 2011, (postactivation follow-up evaluation), the subject reported feeling faint upon rolling over in bed at night and when rising from bed, in addition to some spinning sensation when changing positions. At the 3-month evaluation, June 1, 2011, a change in hearing was documented in the implanted ear (57.4 dB poorer than preoperative levels), resulting in profound loss of hearing. Another course of steroids was prescribed, with the same dosage and regimen as the first. An email communication, September 1, 2011, from the subject's daughter via the subject's clinician indicated that the dizziness had resolved but not the hearing loss. Further follow-up confirmed that the dizziness had resolved by the 6-month study evaluation, September 6, 2011. Significant improvements in acoustic thresholds were also noted, over the range 125 through 1000 Hz, of up to 20 dB. However, the average loss over this range remained 43 dB poorer than preoperative levels, resulting in a profound loss of hearing at 6 months postactivation. At the 12-month evaluation audiometric measures showed further improvement in low-frequency hearing, now 37 dB poorer than preoperative measures. However, the low-frequency hearing loss remained in the profound range, confirmed more recently on August 28, 2012, 18 months postactivation.

Based on responses to the Device Use Questionnaire at 6 and 12 months postactivation, the subject was dissatisfied with device outcomes. At the 12-month evaluation, the most recent evaluation when speech perception is measured per protocol, [redacted] scored 15% for the CNC word test in Hybrid Mode (7% Cochlear Implant Alone) compared with 21% Acoustic Alone in the implanted ear, preoperatively. In the Combined Mode the subject scored 53% (49% Bimodal Mode) compared with 48% preoperatively using the Bilateral Acoustic mode. Speech understanding in noise, as measured using the AzBio sentence test, was 12.5% preoperatively Acoustic Alone in the ear-to-be implanted and 0.0% with the cochlear implant alone at the 12-month postactivation evaluation. When using the Hybrid cochlear implant in the Combined Mode the subject scored 6.5% compared with 24.7%, preoperatively, with the Bilateral Acoustic mode.

Unfortunately, this subject passed away from natural causes, unrelated to the device, January 6, 2013 and no further updates were available after this date.

Subject [redacted]

Surgery Date: May 9, 2011

Date of Occurrence: December 4, 2012

Issue: Profound/Total Loss of Hearing

Status: Closed, Not Resolved

At initial activation, June 9, 2011, subject [redacted] reported to the clinic with a change in low-frequency hearing of 22 dB relative to preoperative measures. However, by the 3-month evaluation on September 8, 2011, the hearing loss had progressed to a pre-to-postoperative change of 36 dB, though not profound in degree. Prednisone at 60 mg with a tapered regimen over 13 days (60 mg for 7 days, tapered from day 8 for 6 days). Low-frequency hearing remained stable, at a severe level, with the subject showing a 37 dB decline in low frequency hearing pre- to postoperatively at the 6 and 12 month evaluations, on December 5, 2011 and June 12, 2012, respectively. By December 4,

2012, 18 months postactivation, low-frequency hearing was at a profound level with a LF PTA of 94 dB HL.

Based on responses to the Device Use Questionnaire, the subject was neutral with regards to device outcomes at 6 months and dissatisfied at 12 months postactivation. At the 12-month evaluation, the most recent evaluation when speech perception is measured per protocol, [redacted] scored 48% for the CNC word test in Hybrid Mode (56% Cochlear Implant Alone) compared with 15% using Acoustic Alone in the implanted ear, preoperatively. In the Combined Mode the subject scored 68% (69% Bimodal Mode) compared with 45% preoperatively using the Bilateral Acoustic mode. Speech understanding in noise, as measured using the AzBio sentence test, was 0% preoperatively Acoustic Alone in the ear-to-be implanted and 0% in the Hybrid Mode at the 12-month postactivation evaluation. When using the Hybrid cochlear implant in the Combined Mode the subject scored 7% compared with 13.7%, preoperatively, with the Bilateral Acoustic mode.

Subject [redacted]

Surgery Date: December 16, 2008

Date of Occurrence: February 10, 2011

Issue: Profound/Total Loss of Hearing, Increased Tinnitus, Dizziness

Status: Closed Not Resolved; Tinnitus and Dizziness Resolved,

At the 24-month follow-up interval February 10, 2011, the site reported that [redacted] woke up in the night, August 18, 2010, hearing a loud noise in the implanted ear (attributed by the subject's clinician to tinnitus) and feeling dizzy ("head felt funny"). Tinnitus was noted to be loud reducing to "quiet" tinnitus in about a day. The subject went to see a primary care physician within a few days of the event. Otoscopic examination revealed nothing remarkable and no treatment was initiated. The subject called the study site audiologist and physician and a 60 mg taper of Prednisone was

prescribed. The study site saw the subject September 7, 2010 and a 15 dB decrease in hearing over that observed at prior assessments was noted, resulting in a severe degree of low-frequency hearing loss. By the February 10, 2011 visit, the tinnitus was reported to have improved considerably and similar in level to that reported preoperatively. The "funny feeling" was reported to still be present intermittently and hearing was still decreased. At the February 10, 2011 evaluation, audiometric testing showed that low-frequency audiometric thresholds were 35 dB poorer than preoperatively. The dizziness was reported to have resolved at a follow-up evaluation that took place January 31, 2013. At this time, the subject presented with a profound loss of low-frequency hearing (57.4 dB poorer than preoperatively).

Based on responses to the Device Use Questionnaire, the subject was very satisfied with regards to device outcomes at 6 months and 12 months postactivation. At the 12-month evaluation, the most recent evaluation when speech perception is measured per protocol, [redacted] scored 87% for the CNC word test in Hybrid Mode (75% electric stimulation alone) compared with 46% using Acoustic Alone in the implanted ear, preoperatively. In the Combined Mode the subject scored 87% (83% Bimodal Mode) compared with 47% preoperatively using the Bilateral Acoustic mode. Speech understanding in noise, as measured using the AzBio sentence test, was 34.4% preoperatively Acoustic Alone in the ear-to-be implanted and 84.0% in the Hybrid Mode at the 12-month postactivation evaluation. When using the Hybrid cochlear implant in the Combined Mode the subject scored 85.8% compared with 37.0%, preoperatively, with the Bilateral Acoustic mode.

Subject [redacted]

Surgery Date: October 16, 2008

Date of Occurrence: February 18, 2009

Issue: Profound/Total Loss of Hearing

Status: Closed, Not Resolved

Subject [redacted], showed a low-frequency average decrease in hearing thresholds of 76 dB by 12 months postactivation, on November 17, 2009, which resulted in a total hearing loss in the low-frequency threshold range. Consequently, this subject did not use the Acoustic Component of the Hybrid implant system. A change in hearing was first reported at the Initial Activation, November 17, 2008 with an average loss of 34 dB, and loss progressed to 48 dB at 3 months, February 18, 2009 by which time the low-frequency hearing loss was profound in degree. By May 17, 2011, 30 months postactivation, the subject presented with a complete loss of hearing. At the most recent 36-month postactivation follow-up, December 22, 2011, the subject again presented with a complete loss of residual hearing.

Based on responses to the Device Use Questionnaire, the subject was satisfied with regards to device outcomes at 6 months and 12 months postactivation. At the 12-month evaluation, the most recent evaluation when speech perception is measured per protocol, [redacted] scored 78% for the CNC word test in the cochlear implant alone mode compared with 24% using Acoustic Alone in the implanted ear, preoperatively. In the Bimodal Mode the subject scored 97% compared with 53% preoperatively using the Bilateral Acoustic mode. Speech understanding in noise, as measured using the AzBio sentence test, was 20.2% preoperatively Acoustic Alone in the ear-to-be implanted and 83.3% in the cochlear implant alone mode at the 12-month postactivation evaluation. When using the Hybrid cochlear implant in the Bimodal Mode the subject scored 88.5% compared with 49.0%, preoperatively, with the Bilateral Acoustic mode.

Subject [redacted]

Surgery Date: August 31, 2011

Date of Occurrence: October 7, 2011

Issue: Profound/Total Loss of Hearing

Status: Closed, Not Resolved

At initial activation, October 7, 2011, a change in low-frequency hearing of more than 30 dB was documented for [redacted] resulting in a complete loss of acoustic hearing (no measurable thresholds at any audiometric frequency). The subject first noticed a change in hearing September 14, 2011. The study site reported that no actions were taken to recover hearing and that the loss appeared to be stable as of the programming follow-up visit on October 14, 2011. The subject's hearing loss has remained complete up to the 6-month evaluation made April 6, 2012. [redacted] withdrew from the study prior to reaching the 12-month evaluation after being diagnosed with pancreatic cancer.

Based on responses to the Device Use Questionnaire, the subject was very satisfied with regards to device outcomes at 6 months and 12 months postactivation. At the 6-month evaluation, [redacted] scored 18% for the CNC word test in the cochlear implant alone mode compared with 12% using Acoustic Alone in the implanted ear, preoperatively. In the Bimodal Mode the subject scored 80% compared with 38% preoperatively using the Bilateral Acoustic mode. Speech understanding in noise, as measured using the AzBio sentence test, was 0% preoperatively Acoustic Alone in the ear-to-be implanted and 0% in the cochlear implant alone mode at the 6-month postactivation evaluation. When using the Hybrid cochlear implant in the Bimodal Mode the subject scored 43.4% compared with 7.7%, preoperatively, with the Bilateral Acoustic mode.

Subject [redacted]

Surgery Date: September 27, 2011

Date of Occurrence: November 1, 2011

Issue: Profound/Total Loss of Hearing

Status: Closed, Not Resolved

At initial activation, November 1, 2011, a change in low-frequency hearing of more than 30 dB was documented for [redacted] first noted October 23, 2011, resulting in a profound loss of acoustic hearing. The study site reported that no actions were taken to

recover hearing and that the loss appeared to be stable as of the programming follow-up visit on November 21, 2011. By the 3-month evaluation, January 31, 2012, the hearing loss had progressed such the [redacted] presented with a total loss of low-frequency hearing, which has remained the case per the 12-month evaluation made November 20, 2012.

At the 3-month evaluation, [redacted] scored 69% for the CNC word test in the cochlear implant alone mode compared with 59% using Acoustic Alone in the implanted ear, preoperatively. In the Bimodal Mode the subject scored 85% compared with 27% preoperatively using the Bilateral Acoustic mode. Speech understanding in noise, as measured using the AzBio sentence test, was 13.1% preoperatively Acoustic Alone in the ear-to-be implanted and 74.2% in the cochlear implant alone mode at the 3-month postactivation evaluation. When using the Hybrid cochlear implant in the Bimodal Mode, the subject scored 75.6% compared with 20.4%, preoperatively, with the Bilateral Acoustic mode.

At the 6-month evaluation, May 10, 2012, [redacted] presented with decreased performance in the implanted ear, which the clinician ascribed to be possibly related to changes in impedance levels. The subject scored 18% for the CNC word test in the cochlear implant alone mode, a significant decrease compared with 69% at the 3-month interval. In the Bimodal Mode the subject scored 82%, similar to that reported at the 3-month evaluation. Speech understanding in noise, as measured using the AzBio sentence test, was 13.1% preoperatively Acoustic Alone in the ear-to-be implanted and 0% in the cochlear implant alone mode at the 6-month postactivation evaluation. When using the Hybrid cochlear implant in the Bimodal Mode the subject scored 29.5% compared with 20.4%, preoperatively, with the Bilateral Acoustic mode. The subject was seen again May 15, 2012 after programming adjustments and the subject obtained an improved score of 44% for the CNC test cochlear implant alone, more consistent with that observed at the 3-month evaluation.

[redacted] was evaluated at 12 months postactivation, November 20, 2012. Subject [redacted] scored 16% for the CNC word test in the cochlear implant alone mode compared with 59% using Acoustic Alone in the implanted ear, preoperatively. In the Bimodal Mode the subject scored 80% compared with 27% preoperatively using the Bilateral Acoustic mode. Speech understanding in noise, as measured using the AzBio sentence test, was 13.1% preoperatively Acoustic Alone in the ear-to-be implanted and 15.6% in the cochlear implant alone mode at the 12-month postactivation evaluation. When using the Hybrid cochlear implant in the Bimodal Mode, the subject scored 88.1% compared with 20.4%, preoperatively, with the Bilateral Acoustic mode. Based on responses to the Device Use Questionnaire, the subject was dissatisfied with regards to device outcomes at 6 months and 12 months postactivation.

Subject [redacted]

Surgery Date: June 15, 2011

Date of Occurrence: June 16, 2011

Issue: Profound/Total Loss of Hearing

Status: Closed, Not Resolved

Immediately following surgery, June 16, 2011, this subject experienced a significant change in hearing resulting in a complete loss of residual hearing in the implanted ear. The subject was administered 60 mg of Prednisone for 7 days with no tapering but serial audiograms taken June 23, June 27 and June 29, 2011, showed no improvement in hearing. By device activation, on July 15, 2011, hearing thresholds were measurable but of a profound degree. Aided word recognition for the implanted ear (acoustic alone) was reported to be 0% compared with 49%, preoperatively.

At the 3-month postactivation interval, October 24, 2011, it was reported that the subject had a bicycle accident in which [redacted] impacted the head on the implanted side. The subject was wearing a helmet. During this evaluation low-frequency thresholds were

noted to be poorer. At initial activation low-frequency hearing was at profound levels and nonmeasurable by 3 months postactivation. Given the progression in hearing loss by initial activation a connection between the accident and further changes in hearing is not clear.

Based on responses to the Device Use Questionnaire, the subject was satisfied with regards to device outcomes at 6 months and very satisfied at 12 months postactivation. At the 12-month evaluation, [redacted] did not make use of the acoustic component and scored 77% for the CNC word test in the cochlear implant alone mode. This compares with a score of 49% using Acoustic Alone in the implanted ear, preoperatively. In the Bimodal Mode, the subject scored 84% compared with 55% preoperatively using the Bilateral Acoustic mode. Speech understanding in noise, as measured using the AzBio sentence test, was 26.7% preoperatively Acoustic Alone in the ear-to-be implanted and 78.5% in the cochlear implant alone mode at the 12-month postactivation evaluation. When using the Hybrid cochlear implant in the Bimodal Mode, the subject scored 89.2% compared with 57.7%, preoperatively, with the Bilateral Acoustic mode.

Subject [redacted]

Surgery Date: October 25, 2010

Date of Occurrence: February 8, 2011

Issue: Profound/Total Loss of Hearing

Status: Closed, Not Resolved

One month after device activation, January 5, 2011, the patient reported a possible change in hearing. On January 24, 2011, a conductive hearing loss was suspected and a course of antibiotics (Augmentin) and steroids (Prednisone) was prescribed. The dosage for both medications was 60 mg for 5 days, tapered over the next 6 days; 30 mg for 3 days, 20 mg for 2 days, and 10 mg for 2 days. However, by February 8, 2011 the hearing loss in the low frequencies was confirmed as sensorineural with a profound low-

frequency hearing loss being documented in the implanted ear. Steroids were again administered with no improvement noted. By April 27, 2011, 4 months after device activation, hearing in the implanted ear had further decreased, still at a profound level of loss. At the 6-month evaluation, June 29, 2011, a complete loss of hearing was noted in the implanted ear. [redacted] does not use the Hybrid sound processor acoustic component.

Based on responses to the Device Use Questionnaire, the subject was neutral with regards to device outcomes at 6 months and 12 months postactivation. At the 12-month evaluation, the subject scored 46% for the CNC word test Cochlear Implant Alone compared with 19% using Acoustic Alone in the implanted ear, preoperatively. In the Bimodal Mode the subject scored 63% compared with 36%, preoperatively, using the Bilateral Acoustic mode. Speech understanding in noise, as measured using the AzBio sentence test, was 12.9% preoperatively Acoustic Alone in the ear-to-be implanted and 17.9% electric alone at the 12-month postactivation evaluation. However, when using the cochlear implant with the contralateral hearing aid (Bimodal Mode) the subject scored 53.7%, compared with 32.9% preoperatively with the Bilateral Acoustic mode.

Subject [redacted]

Surgery Date: March 30, 2011

Date of Occurrence: May 6, 2011

Issue: Profound/Total Loss of Hearing

Status: Closed, Not Resolved

Subject [redacted] showed a decrease in low-frequency hearing thresholds of 22.5 dB, by initial activation on May 6, 2011 and was treated with Prednisone at 60 mg per day with no taper since changes of > 30 dB were observed over 125 to 500 Hz. At this time the loss of hearing was profound in nature (averaged over 250 through 1000 Hz, since 125 Hz was indicated as vibrotactile at 45 dB HL). The subject reported noticing a

change in hearing April 12, 2011. Hearing thresholds showed some improvement at 3 months postactivation. However, by the 6-month postactivation evaluation, November 9, 2011, the hearing loss had progressed to a profound low-frequency range hearing loss, corresponding to a 45 dB decrease relative to preoperative hearing. Based on the most recent follow-up evaluation (18 months postactivation), October 26, 2012, hearing has remained stable (a 39 dB decrease compared with preoperative levels).

Based on responses to the Device Use Questionnaire, the subject was very satisfied with regards to device outcomes at 6 months and 12 months postactivation. At the 12-month evaluation, the most recent evaluation when speech perception is measured per protocol, CNC word recognition in Hybrid Mode was 44% (49% CI alone) compared with 11% preoperatively using Acoustic Alone. Bilaterally, this subject scored 69% on CNCs in the Combined Mode (73% CI alone) compared with 27% preoperatively with the Bilateral Acoustic mode. For the AzBio test in noise, this subject scored 4.0% in the Hybrid Mode compared with 4.9% Acoustic Alone, preoperatively in the ear-to-be implanted. In the Combined Mode, [redacted] scored 35.1% compared with 9% preoperatively, using two hearing aids.

Subject [redacted]

Surgery Date: July 8, 2009

Date of Occurrence: August 17, 2010

Issue: Profound/Total Loss of Hearing

Status: Closed, Not Resolved

Subject [redacted] showed a decrease in low-frequency hearing thresholds of more than 30 dB, about 2 weeks after surgery and was treated with 60 mg of Prednisone for 18 days, tapered from day 7 for 6 days . By the initial activation, August 3, 2009, a change in average low-frequency hearing of 35 dB was reported, resulting in a severe degree of low-frequency hearing loss. Hearing thresholds remained stable at 3 and 6 months

postactivation. By the 12-month postactivation evaluation, August 17, 2010, the hearing loss progressed to a profound low-frequency range hearing loss, corresponding to a 57 dB decrease relative to preoperative hearing. Based on the most recent follow-up evaluation (42 months postactivation), March 21, 2013, hearing has remained stable (a 60.4 dB decrease compared with preoperative levels).

Based on responses to the Device Use Questionnaire, the subject was dissatisfied with regards to device outcomes at 6 months and very dissatisfied at 12 months postactivation. At the 12-month evaluation, the most recent evaluation when speech perception is measured per protocol, CNC word recognition in Hybrid Mode was 66% (68% CI alone) compared with 40% preoperatively using Acoustic Alone. Bilaterally, this subject scored 80% on CNCs in the Combined Mode (78% CI alone) compared with 46% preoperatively with the Bilateral Acoustic mode. For the AzBio test in noise, this subject scored 76% in the Hybrid Mode compared with 27.2% Acoustic Alone, preoperatively in the ear-to-be implanted. In the Combined Mode, [redacted] scored 69.9% compared with 31.9% preoperatively, using two hearing aids.

Subject [redacted]

Surgery Date: January 12, 2011

Date of Occurrence: February 10, 2011

Issue: Profound/Total Loss of Hearing

Status: Closed, Not Resolved

A change in low-frequency hearing of more than 30 dB was recorded, audiometrically, in the implanted ear at device activation, February 10, 2011, resulting in a profound degree of hearing loss. Steroid treatment was not indicated. At the 24-month postactivation follow up on March 15, 2013 the subject continued to present with a profound degree of hearing loss.

Based on responses to the Device Use Questionnaire, the subject was satisfied with regards to device outcomes at 6 months and very satisfied at 12 months postactivation. At the 12-month evaluation, [redacted] scored 84% for the CNC word test in the Hybrid Mode (84% electric alone) compared with 42% using Acoustic Alone in the implanted ear, preoperatively. In the Combined Mode the subject scored 70% (Bimodal Mode 77%) compared with 56%, preoperatively, using the Bilateral Acoustic mode. Speech understanding in noise, as measured using the AzBio sentence test, was 63.5% preoperatively Acoustic Alone in the ear-to-be implanted and 85.8% in the Hybrid Mode at the 6-month postactivation evaluation. When using the Hybrid cochlear implant in the Combined Mode the subject scored 77.7% compared with 63.3%, preoperatively, with the Bilateral Acoustic mode.

5.9.8.2.2.12 Reimplantation after Profound or Total Loss of Low-Frequency Hearing

Four subjects, [redacted] underwent revision surgeries to have the Hybrid L24 implant replaced with a traditional cochlear implant. All 4 cases experienced profound hearing loss postoperatively and dissatisfaction with the performance of the Hybrid implant. In addition, subject [redacted] had a suspected device issue related to partial electrode shorting across most of the Hybrid electrode array (described above under 5.9.8.2.1.4 Partial Short-Circuited Electrodes).

Subject [redacted]

Surgery Date: February 26, 2011

Date of Occurrence: September 20, 2011

Date of Revision Surgery: February 6, 2013

Issue: Profound/Total Loss of Hearing

Status: Closed, Not Resolved

At initial activation, March 22, 2011, subject [redacted] presented with a change in low-frequency hearing of 12 dB relative to preoperative measures. However, by the 3-month evaluation on June 10, 2011, the hearing loss had progressed to a pre-to-postoperative change of 26 dB, which resulted in a severe degree of low-frequency hearing loss. By the 6-month evaluation, September 20, 2011, a further progression was documented such the degree of low-frequency hearing loss was profound in degree. The change in hearing was reported as being first noticed by the subject sometime in July of 2011. Steroid therapy was not initiated as the subject had a prior negative reaction to steroids and refused further treatment with oral steroids. At the 12-month evaluation, March 21, 2012, [redacted] presented with a profound hearing loss in the implanted ear.

Based on responses to the Device Use Questionnaire, the subject was dissatisfied with regards to device outcomes at 6 months and very dissatisfied at 12 months postactivation. At the 12-month evaluation, the most recent evaluation when speech perception is measured per protocol, [redacted] scored 5% for the CNC word using Cochlear Implant Alone (no longer using the acoustic component) compared with 14% using Acoustic Alone in the implanted ear, preoperatively. In the Bimodal Mode the subject scored 44% compared with 33% preoperatively using the Bilateral Acoustic mode. Speech understanding in noise, as measured using the AzBio sentence test, was 7.7% preoperatively Acoustic Alone in the ear-to-be implanted and 0.0% in the Cochlear Implant Alone at the 12-month postactivation evaluation. When using the Hybrid cochlear implant in the Bimodal Mode the subject scored 11.3% compared with 12.5%, preoperatively, with the Bilateral Acoustic mode.

By the time the subject reached 18 months postactivation, a decision was made by [redacted] to seek reimplantation with a CI24RE (Freedom) cochlear implant. Surgery took place February 6, 2013 to successfully replace the Hybrid L24 device. One month postactivation of the more recent device the subject scored 26% for CNC words with the cochlear implant alone and 54% using the implant with acoustic hearing in the other ear (Bimodal Mode). Speech understanding in noise, as measured using the AzBio sentence

test, was 10.5% in the cochlear implant (CI) mode at the 1-month post-revision evaluation, compared with 7.7% preoperatively and 0% prior to revision. When using the CI24RE cochlear implant in the Bimodal Mode the subject scored 6.3% compared with 12.5%, preoperatively, with the Bilateral Acoustic mode.

Subject [redacted]

Surgery Date: May 4, 2011

Date of Occurrence: May 25, 2011

Date of Revision Surgery: July 18, 2012

Issue: Profound/Total Loss of Hearing

Status: Closed, Not Resolved

A significant change in hearing was documented at the initial activation, May 25, 2011 and reported as first noticed by the subject May 12, 2011. At that time, low-frequency hearing thresholds had decreased such that the subject had a profound loss in the 125 to 1000 Hz range. Steroid treatment was administered (Prednisone, 20 mg, twice per day for 7 days) but by the postactivation follow-up visit, June 1, 2011, the investigator reported a complete loss of residual hearing. At the 6-month evaluation, December 6, 2011, [redacted] presented with a profound degree of hearing loss. By the 12-month evaluation, June 11 2012, [redacted] presented with a total loss of low-frequency hearing.

By the 6-month evaluation, [redacted] no longer made use of the acoustic component of the Hybrid sound processor and was assessed using the cochlear implant alone in the implanted ear and in the Bimodal Mode. Based on responses to the Device Use Questionnaire, the subject was dissatisfied with regards to device outcomes at 6 months and very dissatisfied at 12 months postactivation. At the more recent, 12-month evaluation, the subject scored 29% for the CNC word test with Cochlear Implant Alone compared with 23% using Acoustic Alone in the implanted ear, preoperatively. In the Bimodal Mode, at 12 months postactivation, the subject scored 63% compared with 50%

preoperatively using the Bilateral Acoustic mode. Speech understanding in noise, as measured using the AzBio sentence test, was 0% preoperatively Acoustic Alone in the ear-to-be implanted and 0% in the cochlear implant (CI) mode at the 12-month postactivation evaluation. When using the Hybrid cochlear implant in the Bimodal Mode the subject scored 3.6% compared with 5.0%, preoperatively, with the Bilateral Acoustic mode.

Once the subject completed the 12-month evaluation, a decision was made by [redacted] to seek reimplantation with a CI24RE cochlear implant. Surgery took place July 18, 2012 to successfully replace the Hybrid L24 device. Six months postactivation of the more recent device the subject scored 46% for CNC words with the cochlear implant alone and 79% using the implant with acoustic hearing in the other ear (Bimodal Mode). Speech understanding in noise, as measured using the AzBio sentence test, was 9.2% in the cochlear implant (CI) mode at the 6-month post-revision evaluation, compared with 0% preoperatively and prior to revision. When using the CI24RE cochlear implant in the Bimodal Mode the subject scored 29.3% compared with 5.0%, preoperatively, with the Bilateral Acoustic mode.

Subject [redacted]

Surgery Date: February 10, 2011

Date of Occurrence: July 13, 2011

Date of Revision Surgery: March 8, 2012

Issue: Profound/Total Loss of Hearing, Decreased Performance, Vertigo, Increased Impedances

Status: Change in hearing Closed, Not Resolved; Other symptoms Resolved

A conductive component to this subject's hearing loss was suspected by the clinic in an adverse event report form, April 12, 2011, but not confirmed by tuning fork tests. [redacted] was performing well with the device until the 3-month postactivation evaluation,

June 9, 2011, when a significant change in hearing was observed. The subject reported experiencing vertiginous episodes in the prior 6 weeks, when waking and rising from bed and when walking. However, a profound degree of hearing loss was not documented audiometrically until July 13, 2011. A significant increase in impedances was observed June 9, 2011 and the clinician spent all the evaluation time available instituting sound processor programming changes, to mitigate the resultant electrode compliance issues on certain electrodes.

By July 13, 2011, speech perception testing showed poor word understanding via the Hybrid implant (9% electric alone). At that time, the study site clinician requested an integrity test to confirm device functionality. The integrity test was completed August 3, 2011 and device reprogramming took place. The integrity test results indicated no evidence of device malfunction. The subject left the clinic with a 100 µs pulse-width MAP (sound processor program) and a full-frequency assignment to the electric domain. By the 6-month evaluation, October 12, 2011, the subject's hearing had not improved, although audiometric testing was not completed at this visit due to time constraints associated with clinician efforts to improve the subject's sound processor programming.

At the 6-month evaluation, [redacted] scored 42% for the CNC word test Cochlear Implant Alone (the acoustic component was not used) compared with 33% using Acoustic Alone in the implanted ear, preoperatively. This represented an improvement over the score obtained at 3 months, at 9%. In the Bimodal Mode, the subject scored 86% compared with 57% preoperatively using the Bilateral Acoustic mode and 80% in the Bimodal Mode at 3 months. Speech understanding in noise, as measured using the AzBio sentence test, was 6.1% preoperatively Acoustic Alone in the ear-to-be implanted and 5.1% with the cochlear implant alone at 6 months. When using the Hybrid cochlear implant in the Bimodal Mode the subject scored 46.6% compared with 38.0% with the Bilateral Acoustic mode, preoperatively. AzBio sentences-in-noise performance was not assessed at the 3-month evaluation due to time constraints. [redacted] was not able to

complete self-assessment metrics due to time constraints but based on informal clinician reporting the subject was not satisfied with device outcomes.

On February 27, 2012 the subject's audiologist notified the Sponsor that this subject elected to have the Hybrid L24 cochlear implant explanted. The Hybrid device was removed and [redacted] was reimplanted with a traditional cochlear implant (CI24RE) March 8, 2012. [redacted] was activated March 22, 2012 and within a few days of activation impedances exhibited the same pattern as those around the 3-month interval for the Hybrid trial. At a programming session, March 29, 2012 the subject's threshold levels (25 µs/phase pulse-width) were consistent with those at activation but due to impedance changes the subject program was out of compliance. Programming parameters were changed to include a wider, 50 µs/phase pulse-width. [redacted] was seen for an additional session where threshold and comfort levels were noted to be stable at 50 µs/phase pulse-width, but impedances levels had changed again. The subject's complaint, which brought him in for evaluation on this date, was decreased sound quality, which was rectified by reprogramming.

[redacted] was seen, July 10, 2012, for a 3-month postactivation follow-up using the CI24RE-based system and reported to be doing well. The subject's audiologist reported that impedances fluctuated somewhat but that the subject's cochlear implant program was consistently within compliance using a 50 µs/phase pulse-width MAP. Threshold and comfort levels were reported to be stable and the clinician did not believe that the device was fluctuating in and out of compliance. CNC word recognition was improved over that observed with the Hybrid device immediately prior to reimplantation. With the CI24RE cochlear implant alone, the subject's CNC word recognition score was 68% and 89% in the Bimodal Mode. For the AzBio sentence test in noise scores were 87.5% and 94.3%, for the cochlear implant alone and Bimodal conditions, respectively. The subject was reported to be content with these outcomes.

Subject [redacted]

Surgery Date: January 5, 2011

Date of Occurrence: May 9, 2011

Date of Revision Surgery: June 29, 2011

Issue: Profound/Total Loss of Hearing

Status: Closed, Not Resolved

At programming follow-up, March 1, 2011, a > 30 dB low-frequency hearing loss was reported in the implanted ear. The subject was prescribed 40 mg of Prednisone for 12 days, tapered for 6 days from day 7 with no improvement in hearing noted. At the 3-month postactivation evaluation, May 9, 2011, the subject's low-frequency hearing had decreased 42.4 dB compared with preoperative hearing such the subject had a profound degree hearing loss. On May 18, 2011 it was also determined that the subject's device had partial short-circuited electrodes that resulted in the Hybrid device being explanted. Reimplantation with a Nucleus 5 device was successfully completed June 29, 2011 (see summary of outcomes under 5.9.8.2.1.4 Partial Short-Circuited Electrodes).

At the 3-month evaluation, [redacted] scored 3% for the CNC word test in Hybrid Mode (6% electric stimulation alone) compared with 27% using Acoustic Alone in the implanted ear, preoperatively. In the Combined Mode the subject scored 62% (65% Bimodal Mode) compared with 49% preoperatively using the Bilateral Acoustic mode. Speech understanding in noise, as measured using the AzBio sentence test, was 9.7% preoperatively Acoustic Alone in the ear-to-be implanted and 1.4% with the CI alone (subjects are assessed in the best-listening mode for the AzBio test – electric alone in this case) at the 3-month postactivation evaluation. [redacted] did not complete the 6-month evaluation so further speech perception data were not available beyond 3 months postactivation. In addition, postoperative self-assessment metrics were not completed.

This subject was evaluated, January 17, 2012 , with the Nucleus 5 cochlear implant system after 6 months experience. The scores obtained clearly showed improved

performance when compared with preoperative scores and with scores obtained for the implanted ear alone after 3 months experience with the Hybrid implant. Six months following activation of the Nucleus 5 cochlear implant this subjects scored 43% CNC with the cochlear implant alone, compared with 27% with a hearing aid preoperatively (prior to receiving the Hybrid implant). In the Bimodal condition, [redacted] scored 64% word recognition compared with 49% using bilateral hearing aids prior to receiving the Hybrid implant. Improved scores were also noted for the AzBio sentences in noise test (at +5 dB signal-to-noise ratio). With a hearing aid preoperatively this subject scored 9.7% and 20% with the Nucleus 5 cochlear implant. In the Bimodal condition the subject obtained a score of 35.9% compared with 29.5% with bilateral hearings prior to receiving the Hybrid implant.

5.10 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 Nucleus Hybrid L24 implant system, as an extension of the platform of the Cochlear Nucleus Freedom cochlear implant (P970051/S028), has been well characterized over the years through extensive and rigorous evaluations by the sponsor (and FDA) in numerous manufacturing and design improvements. The stability of the base Freedom cochlear implant design is seen evident in the minimal reports of device-specific manufacturing or design-related adverse events. To quantify this risk-benefit assessment process, the following discussion utilizes the recommended 'Worksheets' from the FDA Guidance,

"Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and *De Novo* Classifications".

5.10.1 Assessment of the Benefit

The measured clinical benefits for these subjects were highlighted in the primary and secondary endpoints and served to show the device's impact on patient communication (i.e. improvement in patient function), patient satisfaction, patient relief from symptoms (i.e. dissatisfaction with hearing aids to satisfaction with L24), and overall improved quality of life.

The subjects experienced:

- A statistically significant benefit from use of the device at the study endpoint interval (6-months) in speech recognition in both the Hybrid (unilateral) and Combined (bilateral) conditions over preoperative performances with hearing aid(s), both for words and phonemes in quiet (CNC test), and for sentences (AzBio) in background noise at +5 dB SNR;
- substantial improvements in aided thresholds in the high-frequency range with the Hybrid compared to the preoperative hearing aid, and,
- positive perceived benefits and satisfaction, in the majority of cases, based on questionnaire data. Additionally, examination of individual data revealed that ≥ 90% of subjects had a postoperative score equal to or better than their preoperative score in the unilateral, Hybrid condition, and 100% in the everyday, Combined condition.

Even considering the group of subjects who experienced a significant (or total) loss of low-frequency residual hearing resulting in their inability to use low-frequency amplification, significant improvements in speech perception outcomes compared to preoperative amplification (hearing aids) were observed in both the unilateral and bilateral conditions.

5.10.2 Assessment of the Risks

The surgical procedure for the Hybrid L24 is basically the same as for the widely marketed Nucleus 24 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 the European 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 are consistent with those from the Freedom clinical study. 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 were Hybrid L24 reports of '…significant loss of residual hearing at the implant ear…' As traditional cochlear implants were expected to eliminate all residual hearing in the implanted ear, assessment of residual hearing after implantation with the Freedom cochlear implant was not a metric gathered during that study and is an important variable in predicting patient outcomes (benefit) with the Hybrid L24.

Four subjects[70] elected to undergo explantation/reimplantation with a cochlear implant having a longer electrode. The risks of a second surgical procedure were no different than those present in current cochlear implant practice. This supports the presumption that this clinical population is representative of the total cochlear implant population.

5.10.3 Additional Factors

In looking at other available therapeutic options, these patients have limited choices. They can choose to do nothing, but the absence of audible mid- to high-frequency sounds will make communication with others difficult, especially when listening in background noise. They can choose to learn speech reading, but it is well known that less than about a

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

third of sound distinctions are visible, even for the best lip reader. They can choose to learn sign language, but this is not a population that is familiar with the Deaf Community, and sign language does not allow them to communicate with the broader hearing population. The most commonly chosen treatment for patients meeting the Hybrid L24 system indications is the use of conventional air-conduction hearing aids. Those who use hearing aids often receive inadequate benefit from them, even when using frequency-transposition algorithms. They exhibit poor speech recognition scores due to loss of perception of important high-frequency speech sounds.

Therefore the Hybrid cochlear implant system represents a new option for this patient population that has shown relatively limited success with the alternative treatment options used to date.

5.10.4 Risk Mitigation

As with other cochlear implants, providing clear and unambiguous surgical instructions within the labeling is appropriate for the otologic 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 22/51 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. Labeling and potential candidate counseling for all cochlear implants has always included appropriate 'Warnings and Precautions' regarding loss of residual hearing but for this intended population it is very important for them to be advised of the risks associated with loss of residual hearing in their implant ear.

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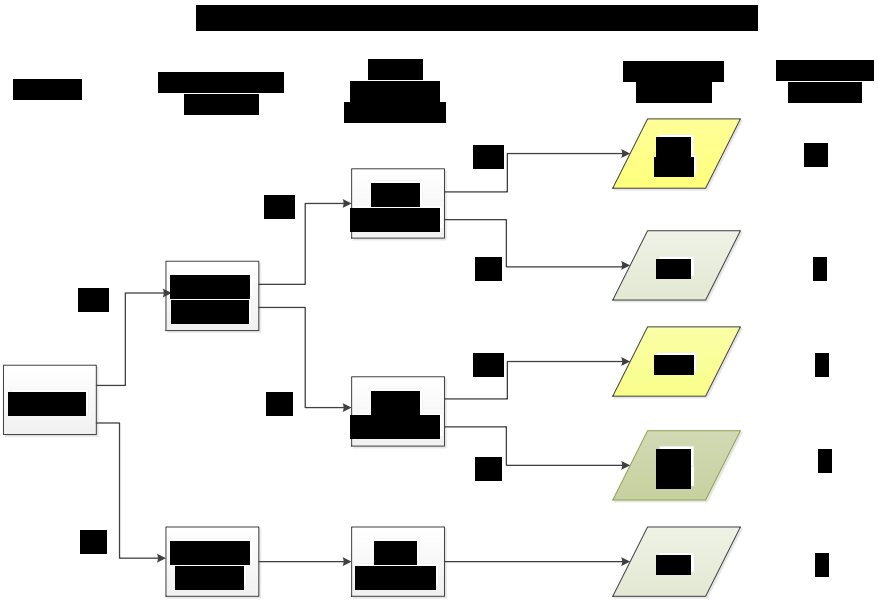

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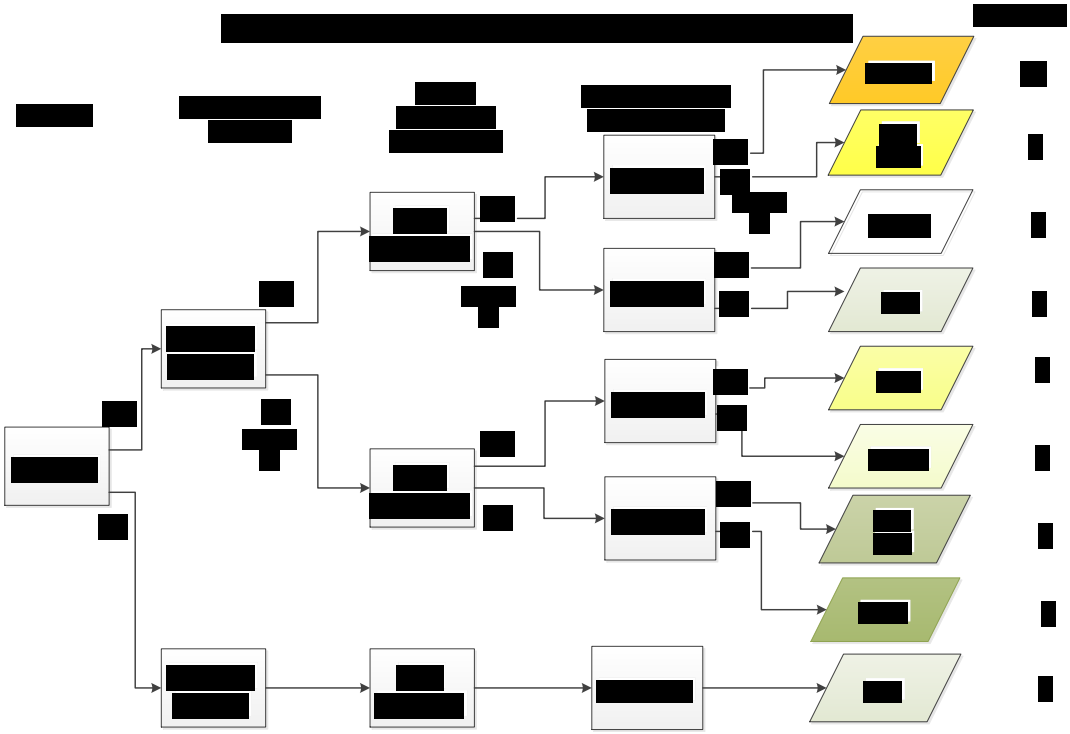

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5.10.6 Summary and Conclusions

The Hybrid L24 Implant represents a new treatment option for a patient population that has few alternatives to treat their hearing loss. The device offers improvements in speech understanding that outweigh the risks associated with surgery and degradation of acoustic hearing in the implanted ear.

Though the primary endpoints of the Hybrid L24 implant were related to the 'hybrid mode', it is important to acknowledge that the Combined Mode, where both ears are used with all available stimulation, is the listening condition normally used by most patients on a daily basis. In considering the risks associated with the study, it is important to consider the impact of the procedure on the patient overall.

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 condition (i.e., with two hearing aids) when tested in the Combined Mode (i.e., both ears acoustically in addition

to the Hybrid cochlear implant) at the 6-month endpoint. Furthermore, quantitative analysis of the risks and benefits associated with the decision to undergo the treatment support implantation in the indicated population.

In accordance with 21 CFR 860.7, valid scientific evidence has been presented in this submission demonstrating that the benefits that the device offers, when used according to instructions in the indicated population, outweigh the risks. The risk benefit analysis supports approval of the device.

5.11 Examination of Individual Subject Data

Appendix 71, Tab 23 contains individual case narratives for each of the 50 subjects implanted with the Nucleus Hybrid L24 Implant System. Each narrative provides a brief summary of outcomes for speech perception, hearing sensitivity, and adverse events observed for each subject. These narratives support that the Hybrid L24 Implant System provides significant benefit for most subjects in terms of device performance and satisfaction.

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