ATTACHMENT 3

Investigational Protocol: Iowa Cochlear Implant Clinical Research Center Hybrid Cochlear Implants in Severe to Profound Adults, Children, and Adolescents

1 INVESTIGATIONAL PROTOCOL

The purpose of this study is to determine if individuals with residual low-frequency hearing in the severe range can develop improved speech perception by combining their residual acoustic hearing with electrical processing through a cochlear implant designed to stimulate the high-frequency basal and middle turn of the cochlea while preserving useful low-frequency acoustic hearing. To accomplish this, we propose to implant individuals with severe hearing with a Cochlear® Nucleus™ Hybrid L24 Implant or a Cochlear® Nucleus™ Hybrid S12 in the poorer ear. We believe these devices will do less damage to the Organ of Corti structures, than longer, more invasive standard cochlear implant electrodes. Two different populations will be studied under this IDE.

Population 1: 15 Adults who have a severe sensorineural hearing loss with a pure-tone average (PTA) between 60-90 dB HL between 125-1500 Hz and profound loss at higher frequencies will be implanted with the Cochlear® Nucleus™ Hybrid L24 Implant. The potential subject will present with Consonant-Nucleus-Consonant (CNC) monosyllabic word scores between 0-35% in the ear to be implanted and up to 60% understanding in the contralateral ear in the best-aided condition.

Population 2: 30 Children (ages 5-12 years) and adolescents (ages 13-15 years) who have a sensorineural hearing loss with a pure-tone average (PTA) between 70-90 dB HL between 125-1500 Hz and profound loss at higher frequencies will be implanted with the Cochlear® Nucleus™ Hybrid L24 Implant or the Cochlear® Nucleus™ Hybrid S12 Implant. Those that have hearing thresholds between 70-90 dB HL at 1500 Hz would be implanted with the less invasive shorter 10 mm Hybrid S12 in attempt to better preserve the middle frequency range. Those with hearing thresholds >90 dB HL at 1500 Hz would receive the longer 16 mm Hybrid L24 electrode. The potential subject will present with Phonetically Balanced Kindergarten (PB-K) monosyllabic word scores between 0-50% in the ear to be implanted and up to 60% understanding in the contralateral ear in the best-aided condition.

Through the preserved acoustic hearing, we believe the subject will experience better signal to noise ratios for speech perception in noise, better localization of sound and an improvement music perception. Histological evidence from patients implanted with standard arrays and our experience with a short electrode array for implantation of individuals with significant residual hearing both support this assumption (Nadol, Shiao, Burgess, Ketten, Eddington et al., 2001). The duration of this study will be 2 years (24 months) for adults and for 5 years (60 months) in children and adolescents.

1.1 *Criteria for Inclusion in Population 1*

Criterion for selection will be subject interest in preservation of residual hearing; severe sensorineural hearing loss; lack of benefit from appropriately fit binaural hearing aids worn on a full-time basis; and realistic expectations. Qualified participants must also meet the following criteria for inclusion:

1. Eighteen year of age or older at the time of implantation.
2. Severe sensorineural hearing loss with a pure-tone average (PTA) between 60-90 dB HL between 125-1500 Hz and profound loss at higher frequencies in the ear to be implanted.

3. Speech Perception:
    a. The Consonant-Nucleus-Consonant (CNC) word recognition score between 0% and 35% inclusive (i.e., 0% ≤ score ≤ 35%) in the ear to be implanted.
    b. The CNC word recognition score in the contralateral ear equal to or better than, in the ear to be implanted but not more than 60% in the best-aided condition.
4. English spoken as a primary language.
5. Willingness to comply with all study requirements.
6. Minimum of 30 day hearing aid trial with appropriately fit hearing aids worn on a full-time basis (8 hours per day).
7. Patient cochlea and normal cochlear anatomy.

1.2 Criteria for Inclusion in Population 2

Criterion for selection will be parent interest in preservation of residual hearing; severe post-lingual onset of sensorineural hearing loss; lack of benefit from appropriately fit binaural hearing aids worn on a full-time basis; and supportive family dynamics. Qualified participants must also meet the following criteria for inclusion:

1. Five to fifteen years of age at the time of implantation.
2. Severe sensorineural hearing loss with a pure-tone average (PTA) between 70-90 dB HL between 125-1500 Hz and profound loss at higher frequencies in the ear to be implanted.
3. Speech Perception:
    a. The Phonetically Balanced-Kindergarten (PB-K) word recognition score between 0% and 50% inclusive (i.e., 0% ≤ score ≤ 50%) in the ear to be implanted.
    b. The PB-K word recognition score in the contralateral ear equal to or better than, in the ear to be implanted but not more than 60%.
4. English spoken as a primary language.
5. Willingness to comply with all study requirements.
6. Minimum of 30-day hearing aid trial with appropriately fit hearing aids worn on a full-time basis (8 hours per day)..
7. Patent cochlea and normal cochlear anatomy.
8. Must be in a habilitation/educational program with an emphasis on spoken language development.

1.3 Criteria for Exclusion in Populations 1 and 2

1. Medical or psychological conditions that contraindicate undergoing surgery.
2. Ossification or any other cochlear anomaly that might prevent complete insertion of the electrode array.
3. Unrealistic expectations on the part of the candidate and/or candidate's family, regarding the possible benefits, risks, and limitations that are inherent to the surgical procedure(s) and prosthetic devices.

4. Unwillingness or inability of the candidate to comply with all investigational requirements.
5. Active middle ear infection.

2 Investigational Procedure

2.1 Design Overview

The study will be conducted as a repeated-measure, single-subject experiment. A single-subject research design (in which each subject serves as his or her own control) is appropriate since it accommodates the heterogeneity that characterizes hearing-impaired populations. Blinding or masking procedures are not included in the design, as it is not possible to conceal the presence or absence of a cochlear implant from device recipients and/or clinical investigators.

Preoperatively, candidates will be assessed with their current amplification to evaluate their appropriateness for entrance into the study. The candidate's audiometric configuration and speech perception must meet the above inclusion criteria. Prior to any speech perception testing taking place, the appropriateness of the hearing aid fitting will be assessed (see below for further details) and adjustments made if necessary. In cases where amplification has not been used for more than one year, new hearing aids will be fitted, worn for a minimum 30-day trial period and the subjects re-evaluated to confirm continuance with the study.

Fifteen adults who have a severe sensorineural hearing loss with a pure-tone average (PTA) between 60-90 dB HL between 125-1500 Hz and profound loss at higher frequencies will be implanted with the Cochlear® Nucleus™ Hybrid L24 Implant. The potential subject will present with Consonant-Nucleus-Consonant (CNC) monosyllabic word scores between 0-35% in the ear to be implanted and up to 60% understanding in the contralateral ear in the best-aided condition.

Fifteen children (ages 5-12 years) and adolescents (ages 13-15 years) who have a sensorineural hearing loss with a *PTA* between 70-90 dB HL between 125-1500 Hz, a hearing *threshold >90 dB HL* at 1500 Hz, and profound loss at higher frequencies will be implanted with the *Cochlear® Nucleus™ Hybrid L24 Implant*. In addition, in attempt to better preserve the middle frequency range, fifteen children (ages 5-12 years) and adolescents (ages 13-15 years) who have a sensorineural hearing loss with a pure-tone average *PTA* between 70-90 dB HL between 125-1500 Hz, a hearing *threshold ≤90 dB HL* at 1500 Hz, and profound loss at higher frequencies will be implanted with the *Cochlear® Nucleus™ Hybrid S12 Implant*. All potential subjects will present with Phonetically Balanced Kindergarten (PB-K) monosyllabic word scores between 0-50% in the ear to be implanted and up to 60% understanding in the contralateral ear in the best-aided condition.

Postoperatively, electric alone, hybrid, and combined listening (i.e., electric and acoustic together) modes will be compared to evaluate the usefulness of adding the electric stimulation while preserving residual hearing for acoustic stimulation. The following defines the various modes referenced throughout the course of this text:

Acoustic Stimulation: Use of the word "acoustic" refers to sound only delivered with amplification.

Electric Stimulation: Use of the word "electric" refers to sound delivered via a cochlear implant only.

Hybrid Stimulation: Use of acoustic hearing, with amplification, in addition to electric hearing via a cochlear implant in the same ear.

Combined Stimulation: Use of acoustic hearing bilaterally, with amplification, in addition to electric hearing via a cochlear implant.

2.2 Device Description

Nucleus Hybrid 24 cochlear implant

The Nucleus Hybrid L24 cochlear implant system comprises:

- Nucleus Hybrid L24 cochlear implant,
- Nucleus Freedom™ for Hybrid sound processor or Nucleus Hybrid SP, and
- Nucleus Custom Sound™ programming software.

The Nucleus Hybrid L24 cochlear implant incorporates an electrode array designed to preserve residual hearing. This has been accomplished by employing a thin, straight, intracochlear electrode array attached to a Nucleus cochlear implant receiver/stimulator (the same as currently used in the approved Nucleus Freedom™ cochlear implant system P970051/S028). The Nucleus Hybrid L24 array has 22 electrodes spread over 16 mm and an anticipated insertion depth of 16 mm. It is slim, with its dimensions ranging from 0.35 x 0.25 mm (at the tip) to 0.55 x 0.4 mm, and designed to minimize lateral wall forces with a stiffened basal section to prevent buckling. A winglet is attached to the electrode lead to allow a better handling of the electrode array and to avoid over insertion. The electrode array also incorporates a collar to prevent over-insertion, or further migration, into the cochlea. The resultant insertion angle is about 280-300° in the scala tympani for the Hybrid L24, as confirmed in temporal bone trials at the Medical University Hannover and the University of Melbourne, compared with an insertion angle of 450° for the Nucleus Contour Advance.

The Nucleus Hybrid L24 is the same device described in IDE No. G070191. See ATTACHMENT 1 for a letter from the Sponsor of IDE No. G070191 authorizing the FDA to review the information in IDE No. G070191 for purposes of the current IDE application. The Nucleus Hybrid L24 electrode array also incorporates a platinum ring immediately proximal to the collar. The ring is positioned such that it is located at the site of entry after insertion of the array into the cochlea. The platinum ring is intended to encourage tissue growth to promote sealing of the entry into the cochlea after insertion, and to fixate the array, at the site of entry, so that it does not migrate into or out of the cochlea once inserted.

Nucleus Hybrid S12 cochlear implant

The Nucleus Hybrid S12 cochlear implant system comprises:

- Nucleus Hybrid S12 cochlear implant,
- Nucleus Freedom™ for Hybrid sound processor or Nucleus Hybrid SP, and
- Nucleus Custom Sound™ programming software.

The Nucleus Hybrid S12 cochlear implant incorporates an electrode array designed to stimulate the high-frequency, basal region of the cochlea while maintaining useful acoustic hearing in the low-frequency, apical region. This has been accomplished by employing a short, thin, straight intracochlear electrode array attached to a Nucleus cochlear implant receiver/stimulator (as used with the current, approved Nucleus Freedom cochlear implant). The electrode array incorporates a collar to prevent over-insertion, or further migration, into the cochlea beyond the point where the basal turn curves into the ascending segment. Thus, the electrode array is placed within the straight segment of the basal turn of the scala tympani via a cochleostomy.

The Nucleus Hybrid S12 is the same device described in IDE No. G070016. See ATTACHMENT 1 for a letter from the Sponsor of IDE No. G070016 authorizing the FDA to review the information in IDE No. G070016 for purposes of the current IDE application. The Nucleus Hybrid S12 electrode array also incorporates a platinum ring immediately proximal to the collar. The ring is positioned such that it is located at the site of the cochleostomy after insertion of the array into the cochlea. The platinum ring is intended to encourage tissue growth to promote sealing of the cochleostomy after insertion, and to fixate the array, at the cochleostomy, so that it does not migrate into or out the cochlea once inserted. The Nucleus Hybrid S12 incorporates a 10-electrode array spread over 5.9 mm with an anticipated insertion depth of 10 mm. The resultant insertion angle is about 195-210° in the scala tympani for the Hybrid S12, compared with an insertion angle of 450° for the Nucleus Contour Advance.

Nucleus Freedom for Hybrid sound processor

The Nucleus Freedom for Hybrid sound processor (SP) is a behind-the-ear (BTE) sound processor developed to provide acoustic and electrical stimulation to hearing-impaired candidates with some low-frequency residual hearing. The Nucleus Freedom for Hybrid sound processor is compatible with the Nucleus Hybrid S12 implant and the Nucleus Hybrid L24 implant, as well as Nucleus 24 and Nucleus Freedom implants with Contour Advance or Straight electrode arrays. See ATTACHMENT 1 for a letter from the Sponsor of IDE No. G070016 and IDE No. G070191 authorizing the FDA to review the information in IDE No. G070016 and IDE No. G070191 for purposes of the current IDE application. The Nucleus Freedom for Hybrid SP is functionally the same as the commercially approved Nucleus Freedom SP (P970051/S028), except that it can be programmed to allow acoustic stimulation. Acoustic stimulation is delivered via an acoustic module, called the Hybrid Receiver-In-The-Ear (RITE). The RITE connects to the sound processor via a cable molded into the earhook of the speech processor, thereby delivering acoustic amplification in a similar way to a conventional hearing aid.

Custom Sound software

Programming of the sound processor is achieved via Custom Sound™ software. Updates to the software with minor modifications may occur over the study period. Custom Sound permits the characterization of both electric and acoustic parameters required for Nucleus Hybrid L24 and S12 programming. The general approach for the electric programming is the same as for traditional cochlear implant recipients except that the software provides more flexible frequency boundary assignments for the 10 or 22 channels of the Nucleus Hybrid cochlear implants. The software provides the ability to specify the cut-off frequency at which acoustic stimulation ends and electric stimulation begins. In addition, the software provides a user interface for the clinician to program amplification characteristics such as gain and maximum output, frequency by frequency.

2.3 Preoperative Procedures

2.3.1 Informed Consent

A pre-operative interview will be conducted by the surgeon and audiologist to inform the potential candidate or parent(s) or legal guardian(s) of the child about all aspects of implantation with the Nucleus Hybrid L24 and S12 cochlear implants, study expectations, number of visits, surgical procedure, as well as the postoperative evaluation schedule. The risks of surgery shall be explained to the candidate or to the parent(s) or guardian(s) as outlined on the Informed Consent and Assent Forms (ATTACHMENT 5A [Adults], 5B [Children and Adolescents], 5C [Assent]). These include the normal risks associated with general anesthetic, as well as other risks such as facial paralysis, dizziness, meningitis, post-operative discomfort, and skin flap complications. The potential limitations and

advantages of implantation with the Nucleus Hybrid L24 or Nucleus Hybrid S12 cochlear implants (e.g. loss of residual hearing) shall also be explained. The potential candidate or parent(s) or legal guardian(s) of the child will be given adequate time to review the Informed Consent Form and given the opportunity to ask questions about the document itself and/or the study prior to signing the Informed Consent and Assent Forms. The candidate or parent(s) or legal guardian(s) of the child will then be given a copy of the signed Informed Consent and Assent Forms.

Note that the Informed Consent and Assent Forms must be reviewed and signed by the relevant parties prior to any study evaluation taking place. Any testing, for screening purposes, completed prior to consent being obtained must be repeated after the participant consents to participation in the study.

2.3.2 Hearing History

Information regarding participant's hearing-history (etiology, onset of hearing loss, duration of severe-to-profound hearing loss, amplification use) is to be reported.

2.3.3 Medical/Surgical History

The participant's medical/surgical history is to be reported and is required in order to determine that the participant is medically suitable for cochlear implantation. Information to be collected may include: the participant's general medical history, medications, radiological information (i.e. x-rays), otologic history, and otologic surgical history.

2.3.4 Fitting of Hearing Aids

To be considered for the study, subjects will be assessed using appropriately fitted behind-the-ear (BTE) or in-the-ear (ITE) hearing aids in each ear. There may be some individuals with very good low-frequency hearing who may prefer and perform comparably with no amplification in one or both ears. For the purposes of this study, subjects will use either their own hearing aids or be fitted with new/replacement aids for candidacy assessment. The decision to replace hearing aids will be based on real-ear measurements. Specifically, the slope of the frequency response of the hearing aid must be within the target specified by the Audioscan Verifit System. If this can not be accomplished with the subject's hearing aids, replacement hearing aids will be used. All speech perception inclusion criteria must be met with the subjects using hearing aids, even if amplification provides no additional benefit over natural acoustic hearing.

If the subject does not use hearing aids on a daily basis, does not own hearing aids, or uses hearing aids that are not appropriately fitted, loaner hearing aids are to be fit and provided by the center. The subject will undergo a minimum 30-day hearing aid trial prior to being further assessed for study candidacy. Subjects must use the hearing aids on a full-time basis (8 hours per day). At the end of the trial period, aided word recognition will be reassessed to ensure that candidacy criteria are met.

The National Acoustics Laboratories' NAL/NL1 hearing aid fitting strategy will be used (Byrne, Parkinson, & Newall, 1990; Dillon, 1999) to assess the degree to which real-ear targets are met for Population 1 (adult subjects). Desired Sensation Level (DSL) method will be used to assess the degree to which real-ear targets are met for Population 2 (children and adolescents). These are the standard hearing aid fitting strategies used for these populations in most hearing aid centers. These prescriptive hearing aid fitting methods will use real-ear measures to verify that the slope of the frequency response is within target. During the fitting process, optimization of the response slope will be the priority for those frequencies where thresholds correspond to useful (or aidable) hearing. Studies (Ching, Dillon, & Byrne, 1998; Hogan & Turner, 1998; Turner & Brus, 2001) have suggested that hearing may be no longer useful for thresholds beyond 55 to 80 dB HL, at least for higher

frequencies. According to Turner (2006), provision of amplification for lower frequencies does not appear to be constrained to the same extent by thresholds for lower frequencies (< 2500 Hz), though no proposal is made as to when such a constraint might occur.

Taking a conservative approach, useful hearing will be defined by hearing thresholds better than 90 dB HL for this study. Hearing levels 90 dB HL or poorer are considered to not be aidable, from an amplification perspective.

It is recognized that prescriptive methods are based on average requirements, and that individuals may find deviations from target values optimal for sound loudness, quality, or clarity. For example, individual adjustments required to relieve occlusion effects will be permitted.

2.3.5 Audiological Assessment

The degree of hearing loss will be determined by standard audiometric technique. Audiological assessment will include unaided and aided audiometric thresholds.

Unaided audiometric thresholds will be obtained for each ear, with insert earphones, when possible, using the standard audiometric technique for pure-tone air-conduction testing. Aided audiometric thresholds will be obtained for each ear in the sound-field using frequency-modulated (FM) noise and using the standard audiometric technique with the speakers positioned at 0° azimuth relative to the subject's head. As these subjects may have some low-frequency hearing bilaterally it is important that appropriate consideration be made for masking/plugging the contralateral ear during aided testing when a unilateral ear is being tested. Testing, for both ears, will include the following:

- Unaided Air Conduction thresholds at 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 Air Conduction thresholds at 125, 250, 500, 750, 1000, 1500, 2000, 3000, and 4000 Hz;
- Tympanometry in each ear.

The CNC word recognition test in quiet (at 60 dB A) will be administered in aided conditions (right hearing aid alone and left hearing aid alone) to adults to determine if a candidate meets the speech perception criteria[1]. Candidates must demonstrate a lack of word understanding, defined as preoperative aided CNC word recognition test recognition scores between 0% and 35% inclusive in the ear to be implanted and ≤ 60% in the contralateral ear. The non-test ear will be plugged for all test conditions.

The PB-K word recognition test in quiet (at 60 dB A) will be administered in aided conditions (right hearing aid alone and left hearing aid alone) to adults determine if a candidate meets the speech perception criteria[2]. Candidates must demonstrate a lack of word understanding, defined as preoperative aided PB-K word recognition test recognition scores between 0% and 50% inclusive in the ear to be implanted and ≤ 60% in the contralateral ear. The non-test ear will be plugged for all test conditions.

[1] For unilateral test conditions, the ear contralateral to the test ear will need to be occluded with sound-attenuated ear plugs for aided speech perception testing.

[2] For unilateral test conditions, the ear contralateral to the test ear will need to be occluded with sound-attenuated ear plugs for aided speech perception testing.

A candidate is only considered enrolled when 1) a properly executed informed consent and assent form has been completed and returned, 2) his/her pre-operative candidacy evaluation is accepted, and 3) both forms have been reviewed and approved by the University of Iowa.

2.3.6 Baseline Testing: Population 1 (Adults)

Once candidacy has been determined, auditory function will be evaluated in order to establish a baseline level on those that meet criteria. The tests will be administered using the same bilateral hearing aids used to determine candidacy. The following battery of measures will be administered:

2.3.6.1 Speech Perception Testing

1. *Consonant-Nucleus-Consonant monosyllabic words* (CNC, Tillman & Carhart, 1966) in quiet. Two lists of CNC words will be administered in each test condition. Testing will be attempted in the ear to be implanted and bilaterally at 60 dBA.

2. *The AzBio sentence* (Spahr & Dorman, 2005) lists were created from a corpus of 1000 sentences recorded by 4 untrained speakers, 2 male and 2 female. The original recordings from each speaker were normalized to be approximately equal in level (dB RMS). The materials were processed using a 5-channel cochlear implant simulation and presented to 15 normal-hearing listeners to determine the average level of intelligibility for each sentence. The results allowed for the creation of 33 lists of 20 sentences. Each list includes 5 sentences from each of the 4 speakers and the average level of intelligibility of each list is 85% +/- 1%. Two lists of the AzBio sentences will be presented at a target presentation level of 60 dBA with a +5 dB signal-to-noise ratio or SNR (i.e., the competitor will be set to 55 dBA). For baseline testing, the target and competitor will be presented from the same speaker at 0° azimuth using appropriately fit hearing aids unilaterally for the ear to be implanted and bilaterally.

3. A *Speech Reception Threshold (SRT)* (Turner et al., 2004) is 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 is delivered under the control of custom software in the presence of either speech (i.e., two competing talkers, one male, and one female) or broad band noise. The speech consists of each competing talker repeating the same sentence (each talker a different sentence) for each stimulus presentation. The level of the competing signal is adaptively varied depending on the subject's response. That is, the level increases (i.e., producing a more aversive signal-to-noise ratio) when a correct response is made and decreased (i.e., producing a less aversive signal-to-noise ratio) when an incorrect response is made. For this study the target stimulus will presented from a loudspeaker located at 0° azimuth at 60 dBA. The competing signal will be directed towards the right ear (90° azimuth) or towards the left ear (270° azimuth). The initial presentation level of the competing signal is more arbitrarily set, but generally at, or close to, the same level as the target level. The level of the competitor is then varied adaptively up or down depending on the subject's response. The level initially varies in 8 dB steps, progressing to 4 dB and finally 2 dB steps. A threshold is established once 14 reversals are obtained. Threshold is calculated as the average of the levels at which each of the last 10 reversals occurred. The competing signal is directed towards a different channel on the audiometer such that the competitor could be presented from either the same location as the target speech signal or from a loudspeaker located elsewhere. A lower signal-to-noise ratio (SNR) to achieve 50% recognition indicated improvement. In other words, equivalent speech understanding is maintained at a more aversive SNR. Testing will be attempted using appropriately fit hearing aids contralaterally to the ear to be implanted and bilaterally.

Care must be taken to plug the contralateral ear, or provide contralateral masking, when a hearing aid is removed for a test condition (e.g. unilateral testing).

2.3.6.2 Localization Testing

1. A multiple loudspeaker *Everyday Sounds Localization Test* (Dunn, Tyler, & Witt, 2005) using 16 different sound items will be administered. Localization performance will be determined by calculating the Average Root Mean Square (RMS)-error in degrees. Testing will be attempted bilaterally using appropriately fit hearing aids at 60 dBA.

2.3.6.3 Music Perception

1. *Real World Melody Recognition* (CMR-R; Gfeller, Olszewski, Turner, Gantz, Oleson, 2006). This test examines the influence of speech and pitch perception in the recognition of excerpts from "real-world" melodies. Testing will be attempted using appropriately fit hearing aids in the ear to be implanted at 70 dBA.

2. *Modified Melodies Test: Nudge 2 (*MMT; Swanson, Dawson, McDermott, 2009). This test assesses the ability of participants to detect pitch errors in two familiar melodies: Old MacDonald and Twinkle Twinkle when specific notes are modified/nudged by 2 semitones. Testing will be attempted using appropriately fit hearing aids in the ear to be implanted at 70 dBA.

3. *Complex-Tone Pitch Discrimination* (CTPD, Gfeller, Turner, Woodworth, Mehr, Fearn, Witt, Stordahl, 2002). This test assesses the participants' ability to discriminate direction of pitch change as a function of interval size (fundamental frequency range, 131-1048 Hz). This adaptive test results in a threshold (across all frequencies) at which the participant is able to achieve 75% accuracy. This is a brief test (5-10 minutes) that can be repeatedly administered in multiple conditions accurately. Testing will be attempted using appropriately fit hearing aids in the ear to be implanted at 70 dBA.

4. *Iowa Test Appraisal of Sound Quality* (ITASQ, Gfeller, Witt, Woodworth, Mehr, and Knutson, 2002). This test evaluates participants' appraisal of timbre and sound quality of music instruments and real-world music with and without lyrics. Using 4 bipolar adjective scales, participants describe the sound quality of the each excerpt and also rank their preference for the sound. Testing will be attempted using appropriately fit hearing aids in the best aided condition at 70 dBA.

2.3.7 Baseline Testing: Population 2 (Children and Adolescents)

2.3.7.1 Speech Perception Testing

1. *Phonetically Balanced-Kindergarten* (PB-K, Haskins, 1949) word test in quiet. The PB-K test has multiple 50 word lists. The test will be scored as total number of words correct as well as phonemically. Testing will be attempted using appropriately fit hearing aids in the ear to be implanted and bilaterally at 60 dBA. This will be administered to children between the ages of 5-6 years.

2. *Consonant-Nucleus-Consonant monosyllabic words* (CNC, Tillman & Carhart, 1966) in quiet. Two lists of CNC words will be administered in each test condition. Testing will be attempted in the ear to be implanted and bilaterally at 60 dBA. This will be administered to children between the ages of 7-15 years.

3. *Computer-assisted Speech Perception Assessment Test* (CASPA, Boothroyd, 2004; Mackersie, Boothroyd, & Minniear, 2001) in noise using 20 sets of 10 CVC words. Testing will be administered to children and adolescents between the ages of 7-15 years at 65 dBA speech level with a +10 signal to noise ratio. Testing will be attempted in the ear to be

implanted and bilaterally. Results will be scored in terms of percent correct whole word and percent correct phonemes.

Care must be taken to plug the contralateral or ipsilateral ear, or provide contralateral masking when testing individual ears.

2.3.7.2 Localization Testing

1. A multiple loudspeaker *Everyday Sounds Localization Test* (Dunn, Tyler, & Witt, 2005) using 16 different sound items will be administered. Localization performance will be determined by calculating the Average Root Mean Square (RMS)-error in degrees. Testing will be attempted bilaterally using appropriately fit hearing aids at 60 dBA to children between the ages of 7-15 years.

2.3.7.3 Speech Language Testing

1. *Peabody Picture Vocabulary Development Scale* (PPVT, Dunn & Dunn, 1997*)*. The PPVT is a standardized, norm-referenced measure of receptive vocabulary skills. The test is a multiple-choice measure consisting of sets of four black and white line drawings. The examiner names one of the pictures and the test recipient is expected to indicate which picture has been labeled, either verbally or through pointing. It is appropriate for children and adults from 2 years, 6 months to 90 years, 11 months of age. Testing will be attempted bilaterally.

2. *Goldman Fristo Test of Articulation* (GFTA, Goldman & Fristoe, 2000). The GFTA-2 is a standardized, norm-based articulation measure that samples spontaneous sound production. Children are asked to respond to picture plates and verbal cues from the examiner with single words that test consonant accuracy in initial, medial, and final positions. This measure has norms based on the performance of normal-hearing children from age 2 years to 21 years. Testing will be attempted bilaterally.

3. *Woodcock Reading Mastery Test* (WRMT-R/NU, Woodcock, 1998). These tests are standardized from kindergarten through high school. The Word Identification and Word Attack subtests from the WRMT-R will be used to assess children's *word recognition* abilities. These subtests measure accuracy of sight word recognition and phonetic decoding of pronounceable non-words. *Reading comprehension* abilities will be assessed by the Passage Comprehension subtest of the WRMT-R. The WRMT-R uses a cloze procedure in which the participants are asked to read a short passage and orally provide a missing word. It is appropriate for children and adults from 5 years, 0 months to 20 years, 0 months of age. Testing will be attempted bilaterally.

4. *Comprehensive Assessment of Spoken Language* (CASL, Carrow- Wolfolk, 1999*)* Carrow-Woolfolk, 1999) is a standardized, norm-referenced measure of oral language skills. It is appropriate for children ages 3 to 21 years of age. The test is composed of core battery of measures which represents different aspects of language categories (semantics, syntax, and pragmatics). Testing will be attempted bilaterally.

2.3.7.4 Music Perception

1. *Complex-Tone Pitch Discrimination* (CTPD, Gfeller, Turner, Woodworth, Mehr, Fearn, Witt, Stordahl, 2002) assesses the participants' ability to discriminate direction of pitch change as a function of interval size (fundamental frequency range, 131-1048 Hz). This adaptive test results in a threshold (across all frequencies) at which the participant is able to achieve 75% accuracy. This is a brief test (5-10 minutes) that can be repeatedly administered in multiple conditions accurately. It is administered in the best aided condition in the ear to be implanted at 70 dBA.

2. *Melody Recognition by Information Level* (MRIL, Olszewski, Gfeller, Froman, Stordahl, Tomblin, 2005) assesses the participants' ability to recognize and identify simple melodies in closed set provided in 4 different formats: sung with video, sung without video, melody with rhythm, and isochronous (melody without rhythm) in random order. Previous research with children and adults who use CIs has shown that while adults with traditional long-electrode cochlear implants are able to perform successfully in three of the four formats (performing poorly on the isochronous condition), adults with short-electrode cochlear implants are able to perform successfully on all formats. Conversely, children with long-electrode devices are only able to perform well on those that include lyrics and perform at or below change on the other two conditions. It is administered in the best aided condition in the ear to be implanted at 70 dBA.

2.3.7.5 Calibration

Speech perception, music perception, and localization tests will be calibrated using a calibration tone (or calibration sound file). A sound-level meter will be used to measure the dBA level of the calibration tone at a distance of 1 meter from the loudspeaker. The loudness will be adjusted through the audiometer or receiver to achieve the desired loudness level for the specific test.

2.3.8 Surgical Procedure

The surgical procedure for the Nucleus Hybrid L24 and Hybrid S12 cochlear implant requires care to prevent inner ear damage. These procedures are the same as described in IDE No. G070191 and G070016. See ATTACHMENT 1 for a letter from the Sponsor of IDE No. G070191 and G070016 authorizing the FDA to review the information in IDE No. G070191 and G070016 for purposes of the current IDE application.

The most important tenets are given below.

1. A complete mastoidectomy with preservation of the cortex in the area of the tegmen mastoideum performed. Completion of exposure, bony work, and soft tissue work before completing the cochleostomy. This includes drilling a seat for the electronic package, harvesting and constructing a temporal fascia washer. The facial recess or posterior tympanotomy must be opened to allow complete visualization of the round window. The overhanging niche of the round window must be removed using a diamond burr completely exposing the entire round window membrane. These steps minimize the open cochlea's exposure to blood and bone dust. A suture is placed through the boney over hang at the tegmen mastoideum to secure the electrode lead prior to placing the electrode in the scala tympani. This suture stabilizes the springy lead of the implant and prevents translational movement in the scala tympani as the electrode is advanced.

2. Minimally traumatic cochleostomy. A strategy similar to that used to perform a 'drill-out' stapedectomy. This includes making sure bleeding is controlled, bone is slowly removed over the area of the cochleostomy leaving the endosteum of the inner ear intact, and not using suction in the area of an open inner ear. The cochleostomy must be placed approximately 1 mm anterior and inferior to the floor attachment of the round window membrane. The promontory of the cochlea in this portion can be more than 1 mm thick. It is suggested that the promontory be saucerized in this region with a 1-mm diamond burr. Placement of the cochleostomy in the anterior-inferior position to the round window membrane avoids damage to the scala media and spiral ligament. The burr should not enter the scala tympani. The endosteum is opened with a 0.2-mm footplate hook. The smallest cochleostomy needed to insert the implant is made (0.7–0.8 mm). No suctioning of the perilymph is permitted.

3. Minimally traumatic insertion. Short lapse of time between opening the cochlea and insertion is emphasized. The electrode is stabilized with a suture at the lateral tegmen

mastoid cortex prior to insertion into the cochlea. Actual insertion of the electrode is slow (30–45 s) to minimize intracochlear trauma. The fascia washer seals the cochleostomy. No further packing in the scala tympani is allowed.

2.4 Postoperative Procedures

2.4.1 Device Activation

One day prior to activation, subjects without a contraindication to glucocorticoid therapy will be started on prednisone 1mg/kg for 1 week. Subjects will be asked to undergo weekly audiometric testing for one month to monitor acoustic hearing. If drops in threshold of 15 dB HL or more at 125, 250, or 500 are observed, additional prednisone 1mg/kg will be prescribed for 14 days with a gradual taper off over the following week.

Electric Fitting:

The participants will be fit with Nucleus Freedom for Hybrid sound processor (or most current combined speech processor) speech processor using a behind-the-ear (BTE) controller or body level controller. Speech processing strategies used with this device will include ACE (RE), ACE, CIS (RE), CIS or SPEAK, which are all FDA approved for adults. Threshold (T) and comfort (C) values will be measured for the electrical stimulation for each of the channels (22 on the Nucleus Hybrid L24 cochlear implant and 10 on the Nucleus Hybrid S12 cochlear implant). Impedance telemetry results using common ground (CG) and monopolar (MP1, MP2 and MP1+2) stimulation modes will also be recorded. This information will be used to program the speech processor and also to monitor the device for possible degradation of function and/or damage to neural elements.

The process of adjusting the speech processor programs might take place over a period of several months for younger children. Play audiometry or standard audiometric techniques will be used, as appropriate for the child's developmental level, to determine electrical threshold levels for the channels in a child's program.

Subjects will receive extensive counseling regarding how the equipment functions, maintenance and troubleshooting of the device.

Acoustic Fitting:

The acoustic component of the Hybrid sound processor will be appropriately fit using the NAL-NL1 for adults and DSL for children and adolescents (as used preoperatively for the acoustic hearing aids) to assess the degree to which real-ear targets are met for each subject. Fitting methodology with the acoustic component of the Hybrid sound processor is unchanged from that of conventional acoustic hearing aids.

The basic programming approach will be to assign frequency channels to the Hybrid electrode array that supplement the acoustic sensitivity. In other words, the frequency assignment of the electrical stimulation will begin at the frequency where acoustic hearing is no longer useful. For this purpose, hearing thresholds greater than 90 dB HL will be considered not useful from an amplification perspective and not aidable acoustically. For example, if the subject's hearing in the implanted ear is more than 90 dB HL for frequencies at and above 1000 Hz (i.e., useful acoustic hearing up to 750 Hz), the lower frequency boundary for electric stimulation will be set as close as possible to 750 Hz (i.e., the last aidable frequency). That is, electrical stimulation will be provided for inputs from around 750 to 8000 Hz and acoustic for frequencies at and below 750 Hz. Thus, there will be minimal overlap between the acoustic and the electric signals.

2.4.2 Programming Follow-up

Following surgical implantation of the device and an adequate healing period, the implants will be activated (usually 4 to 6 weeks after surgery) and programmed. However, prior to the 4-month post-operative evaluation, additional programming follow-up sessions will be scheduled at 2 weeks and 1 month as it is not unusual for threshold and comfort levels to change during the initial postactivation period. The follow-up sessions will allow the participant's T- and C-levels to be checked as well as any programming adjustments to be made based on the participant's initial experience with the device. Electrical impedance measures also will be obtained. Additional programming at additional post-activation intervals will be assessed and conducted as needed.

C-levels will never be set above 200CL on any electrode. If stimulation at 200CL with the default pulse width of 25us does not elicit a maximal loudness percept, the audiologist will widen the pulse width on that channel and resume psychophysical measurements approximately 5CL below an approximately equal charge level. This will entail manually reducing the current level in the following manner:

When pulse duration is increased from:	The audiologist will manually decrease the CL from 200CL to:
25us to 37us	170CL
25us to 50us	155CL
37us to 50us	175CL
50us to 75us	170CL

Parents and professionals working with the children who participate in this study will receive extensive counseling regarding how the equipment functions, maintenance and troubleshooting of the device, and progression of auditory skills of children who cochlear implants. This is accomplished during visits to the center and through in-service training offered locally via the fiberoptic teleconferences.

2.4.3 Audiologic Follow-up

Audiological Testing:

Unaided audiometric thresholds will be obtained for each ear, with insert earphones whenever possible, using the standard audiometric technique for pure-tone air-conduction testing. During the first month after activation of the Hybrid implant, subjects will be seen on a weekly basis to measure residual acoustic hearing. If more than a 10 dB downward threshold shift is identified, oral prednisone 1mg/kg once a day for 7 days will be prescribed. If hearing is regained or continues to fluctuate, the treating physician and the patient would discuss another trial with the prednisone. If after use of the prednisone there is no change in hearing, the prednisone will be stopped. Additional audiologic follow-up will occur at intervals of 3, 6, 12, and 24 months in adults and at intervals of 4, 8, 12, 18, 24 months, and annually thereafter for three years in children and adolescents.

Unaided (and aided if necessary) testing, for both ears, will include the following:

- Unaided Air Conduction thresholds at 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 Air Conduction thresholds at 125, 250, 500, 750, 1000, 1500, 2000, 3000, and 4000 Hz;

Hearing Aid Verification:

A hearing aid check will be completed by the clinician to verify that the contralateral hearing aid and the acoustic component of the Hybrid sound processor for the implanted ear, if used, are functional prior to aided testing. If any significant change in unaided thresholds is noted then the amplification fitting(s) should be re-evaluated and adjustments made if necessary. A significant change for this purpose only is defined as a shift of more than 10 dB (for the better or worse) at two or more (i.e., < 90 dB HL) frequencies. Hearing aid verification will occur at intervals of 3, 6, 12, and 24 months in adults and at intervals of 4, 8, 12, 18, 24 months and annually thereafter for three years in children and adolescents.

2.4.4 Post-operative Testing: Population 1 (Adults)

Testing will be assessed longitudinally 3, 6, 12, and 24 months. Descriptions of tests are provided in the baseline testing section.

2.4.4.1 Speech Perception Testing

Tests will be attempted in the following conditions (unless otherwise noted):

- Electric stimulation alone (Implant only),
- Hybrid stimulation (i.e., Implant + Ipsilateral Hearing Aid),
- Bimodal stimulation (i.e. Implant and Contralateral Hearing Aid)
- Combined stimulation (i.e., Implant + Ipsilateral and Contralateral Hearing Aids).

1. The *CNC Word recognition test* (two lists per condition, at 60 dBA).

2. The *AzBio sentence lists*. Two lists of the AzBio sentences will be presented at a target presentation level of 60 dBA with a +5 dB signal-to-noise ratio or SNR (i.e., the competitor will be set to 55 dBA).

3. A *Speech Reception Threshold* (SRT) test. Tested only at 6 months and 24 months post-operatively in the Combined and Bimodal Conditions.

Care must be taken to plug the contralateral ear, or provide contralateral masking, when a hearing aid is removed for a test condition (e.g. electric stimulation alone).

2.4.4.2 Localization Testing

1. *Everyday Sounds Localization test* attempted in the combined and bimodal conditions at 60 dBA (tested only at 6 months and 24 months post-operatively).

2.4.4.3 Music Perception

1. *Real World Melody Recognition* (CMR-R). This test is administered in the hybrid condition only at 70 dBA to reduce the possibility of a learning effect from repeated exposure in the same test session.

2. *Modified Melodies Test: Nudge 2* (MMT). This test is administered in the hybrid and CI-only condition at 70 dBA.

3. *Complex-Tone Pitch Discrimination* (CTPD). This is a brief test (5-10 minutes) that can be repeatedly administered in multiple conditions accurately. This test is administered in the hybrid and CI-only condition at 70 dBA.

4. *Iowa Test Appraisal of Sound Quality* (ITASQ). This test is administered in the combined condition only at 70 dBA to reflect responses associated with the subject's everyday listening condition.

2.4.5 Post-operative Testing: Population 2 (Children and Adolescents)

Testing will be assessed longitudinally at 4, 8, 12, 18, 24 months and annually thereafter for three years in children and adolescents.

Descriptions of tests are provided in the baseline testing section.

2.4.5.1 Speech Perception Testing

Tests will be attempted in the following conditions (unless otherwise noted):

- Electric stimulation alone,
- Hybrid stimulation (i.e., Implant + Ipsilateral Hearing Aid),
- Combined stimulation (i.e., Implant + Ipsilateral and Contralateral Hearing Aids).

1. *Phonetically Balanced-Kindergarten* (PB-K) word test in quiet. Testing will be administered at 60 dBA to children between the ages of 5-6 years.

2. *Consonant-Nucleus-Consonant monosyllabic words* (CNC) in quiet. Two lists of CNC words will be administered in each test condition. Testing will be administered at 60 dBA to children between the ages of 7-15 years.

3. *Computer-assisted Speech Perception Assessment Test* (CASPA) in noise. Testing will be administered to children and adolescents between the ages of 7-15 years at 65 dBA speech level with a +10 signal to noise ratio.

Care must be taken to plug the contralateral or ipsilateral ear, or provide contralateral masking when acoustic stimulation is not warranted (e.g. testing CI-Only or Hybrid conditions).

2.4.5.2 Localization Testing

1. *Everyday Sounds Localization test* attempted in the combined and bimodal conditions at 60 dBA (tested only at 12 months and 24 months post-operatively).

2.4.5.3 Speech and Language Testing – all administered in the bilateral listening condition at 12 months and annually thereafter.

All tests will be administered in the combined stimulation condition, unless otherwise noted.

1. *Peabody Picture Vocabulary Development Scale* (PPVT*)*

2. *Goldman Fristoe Test of Articulation* (GFTA)

3. *Woodcock Reading Mastery Test* (WRMT-R/NU)

4. *Comprehensive Assessment of Spoken Language* (CASL)

2.4.5.4 Music Perception

1. *Complex-Tone Pitch Discrimination* (CTPD). This is a brief test (5-10 minutes) that can be repeatedly administered in multiple conditions accurately. It is administered in the hybrid and CI-only condition at 70 dBA.

2. *Melody Recognition by Information Level* (MRIL). This test is administered in the only hybrid condition at 70 dBA to reduce the possibility of a learning effect from repeated exposure in the same test session.

2.4.6 Psychophysical and Electrical Impedance Measurements:

The following psychophysical and electrical impedance measurements will be attempted at 3, 6, 12, and 24 months in adults and at 4, 8, 12, 18, 24 months and annually thereafter for three years in children and adolescents.

1. Electrical thresholds measured in current level.
2. Electrical maximum comfort levels measured in current level.
3. Impedance telemetry results using common ground (CG) and monopolar (MP1, MP2, MP1+2) stimulation modes.

2.5 Adverse Effects

Adverse effects are any undesirable clinical or medical occurrence associated with use of the device or participation in the study. Any adverse effects are to be reported to the FDA and our IRB via the "Adverse Effects Form". The Primary Investigator will be required to verify that there are or there are no adverse effects to report.

Adverse effects will be reported if observed, even if acknowledged as risk factors in the consent. Adverse effects include:

1. Sudden changes in residual low-frequency hearing. Specifically, a PTA at 125, 250, 500 HZ that is ≥30 dB HL.
2. Total loss of residual hearing
3. Vertigo, dizziness, or balance problems that did not exist preoperatively or worsened postoperatively
4. Facial nerve problems
5. Meningitis
6. Perilymphatic fistulae
7. Tinnitus that did not exist preoperatively or worsened postoperatively
8. Implant Migration/Extrusion
9. Skin flap problems
10. Device-related/programming problems
11. Infection requiring explantation
12. Device failure requiring explantation

2.6 Unanticipated Adverse Events

Unanticipated adverse device effects refer to any event not identified above that represents a "serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device if that effect, problem or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects." [FDA 21 CFR 812.3(s)]

Investigators are to inform their respective Institutional Review Boards (IRBs) immediately if an unanticipated adverse device effect is suspected (no more than 10 working days after the investigator learns of the effect). If the case is determined to be an unanticipated adverse device effect, the investigator will fill out an "Unanticipated Adverse Device Effect Form." University of Iowa will report the results of an evaluation of the unanticipated adverse device effect to the FDA and all other reviewing IRBs and investigators within 10 working days after first receiving notice of the event.

2.7 Data Analysis for Population 1

In order to assess the feasibility of using the L24 electrode arrays in adults, data will be analyzed individually and with group statistics. We will measure success of this study by assessing speech perception, localization, and music performance as described above in the test descriptions. We will attempt to compare these results with adults implanted with

standard-length devices on one or both ears on the same test measures. Efficacy of the Nucleus Hybrid L24 cochlear implant system will be determined by a comparison of preoperative (best aided) vs. postoperative outcomes measures. Efficacy will also be measure by statistically significant differences between mean, preoperative speech perception scores (best aided) and postoperative scores. The null hypothesis to be tested is that there is no difference for the subjects between their pre- vs. postoperative speech performance

Because this is a feasibility study, we will only be implanting up to 15 adults with the Nucleus Hybrid L24 cochlear implant. We recognize that this small number of subjects may not afford us enough statistical power to adequately answer all questions associated with the feasibility of using a short electrode device for the provision of acoustic and electric sound processing to adults who demonstrate severe sensorineural hearing loss. However, it may lend us foundational knowledge to assess whether the devices are beneficial to this population of adults.

2.8 Data Analysis for Population 2

In order to assess the feasibility of using the Nucleus Hybrid S12 and L24 electrode arrays in children and adolescents, data will be analyzed individually and with group statistics. We will measure success of this study by assessing speech perception, localization, speech/language development, and music performance as described above in the test descriptions. We will attempt to compare these results with age-matched children implanted with standard-length devices on one or both ears on the same speech perception and speech/language measures. Efficacy of the Nucleus Hybrid S12 and L24 cochlear implant systems will be determined by a comparison of preoperative (best aided) vs. postoperative outcomes measures. Efficacy will also be measure by statistically significant differences between mean, preoperative speech perception scores (best aided) and postoperative scores. The null hypothesis to be tested is that there is no difference for the subjects between their pre- vs. postoperative speech performance

Because this is a feasibility study, we will only be implanting up to 15 children (5-12 years of age) or adolescents (13-15 years of age) with the Nucleus Hybrid S12 and 15 children (5-12 years of age) or adolescents (13-15 years of age) with the Nucleus Hybrid L24 cochlear implants. We recognize that this small number of subjects may not afford us enough statistical power to adequately answer all questions associated with the feasibility of using a short electrode device for the provision of acoustic and electric sound processing to children who demonstrate severe sensorineural hearing loss. However, it may lend us foundational knowledge to assess whether the devices are beneficial to this population of children.

2.9 Longer Electrode Array Reimplantation

Some individuals have elected to have the Nucleus Hybrid cochlear implant removed and replaced with a standard, long electrode-array cochlear implant. This has typically been in cases where individuals have experienced a complete loss of residual hearing. It is a case-by-case decision to replace the Hybrid L24 with a standard length implant. The implant only data provided in the unpublished data section demonstrates that the performance is similar to a standard length implant. If the subject is performing at the average performance level one would not necessarily benefit from a change in device.

Additionally, the insertion of an electrode array may alter the perception of speech and other sounds compared to their sound quality prior to implantation, this may be due to the use of an electrode array, and/or changes in residual hearing. Subjects who elect to be implanted with a standard cochlear implant in the test ear, in place of the Nucleus Hybrid L24 or S12 (whichever they are implanted with) cochlear implant, will be required to complete the study protocol as outlined above.

2.10 References

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