



# **P130016**

# **Nucleus® Hybrid™ L24 Implant System**

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PMA Team Leader

Division of Ophthalmic and Ear, Nose and Throat Devices

FDA/CDRH/ODE

November 8, 2013



## FDA Review Team

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# **Cochlear Nucleus<sup>®</sup> Hybrid<sup>™</sup> L24 Implant System: Proposed Indications for Use (IFU)**

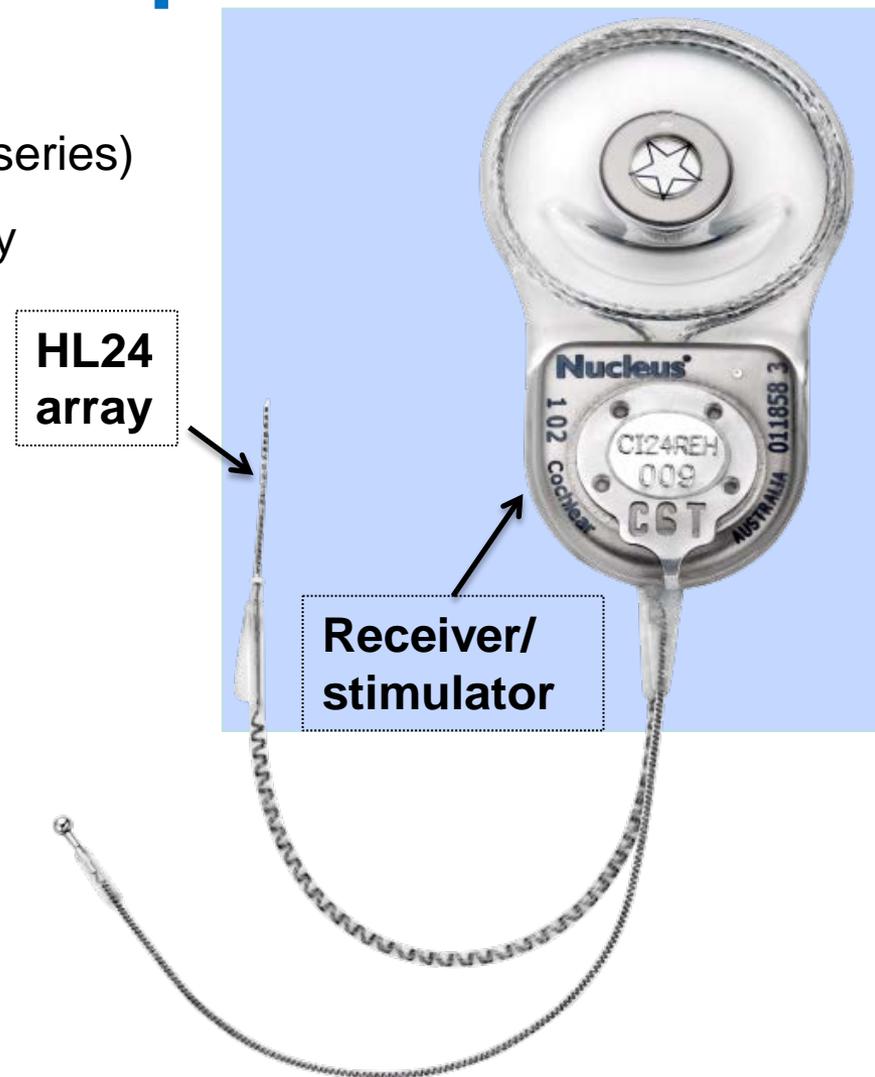
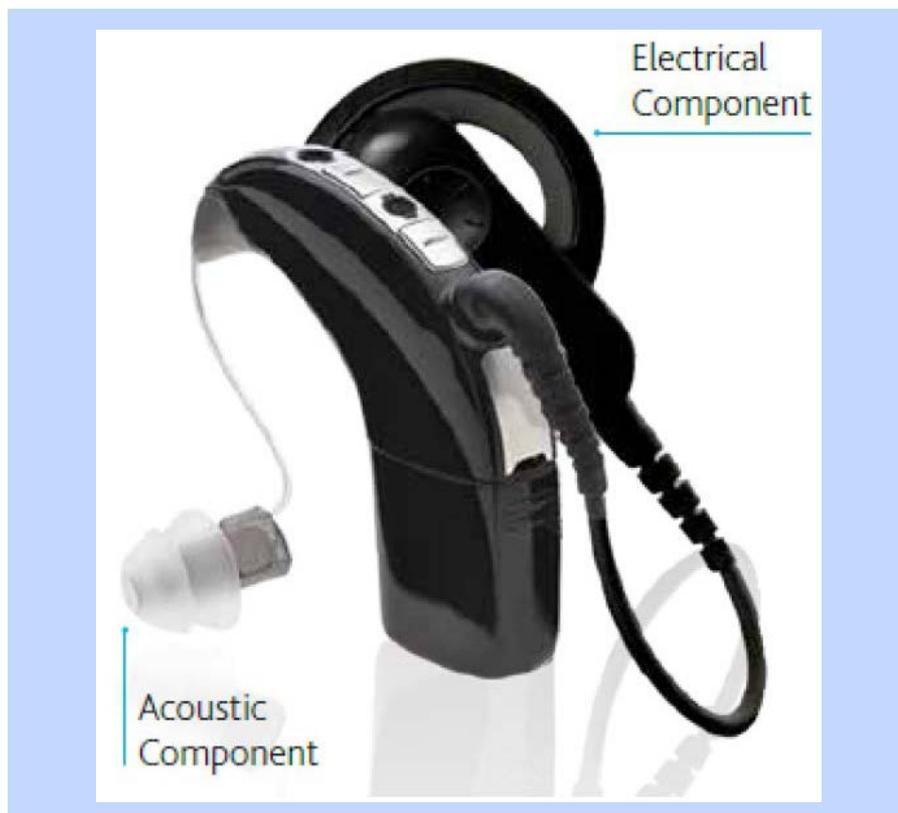
- The Hybrid L24 is indicated for patients 18 years or older who have residual low-frequency hearing sensitivity and bilateral severe to profound high-frequency sensorineural hearing loss, and who obtain limited benefit from bilateral hearing aids.

## Hybrid L24: Proposed IFU (cont'd)

- Typical preoperative hearing loss of candidates ranges from normal to moderate hearing loss in the low frequencies (thresholds no poorer than 60 dB HL at  $\leq 500$  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.

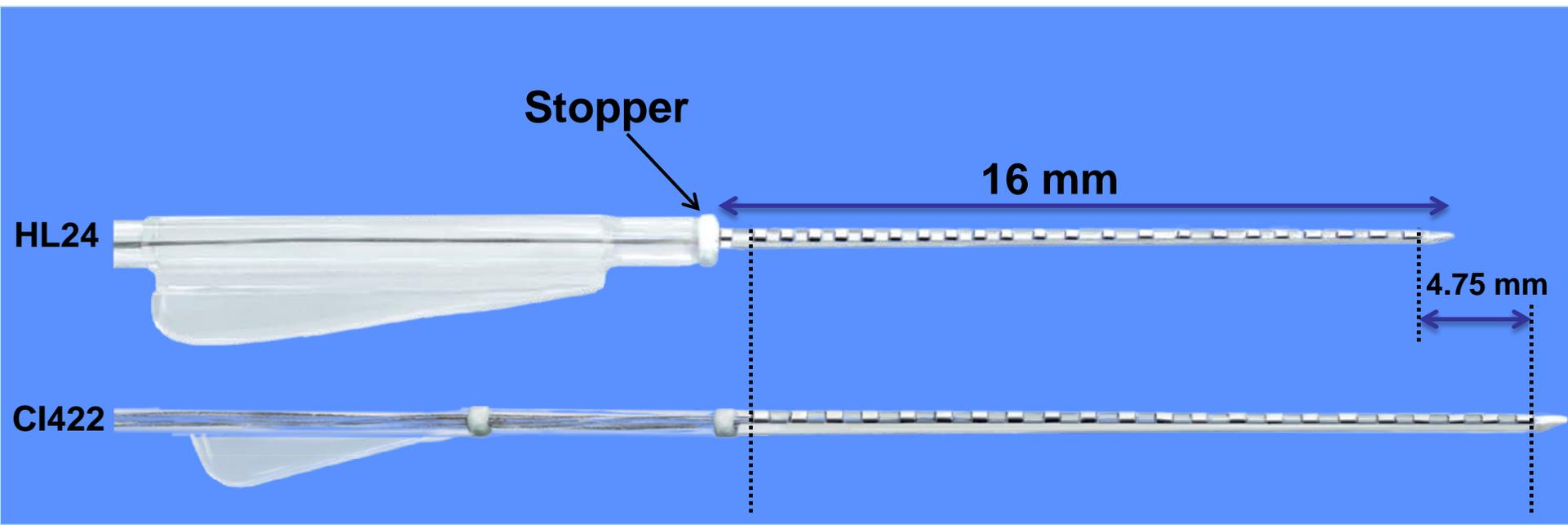
# Device Description

- Hybrid L24 system includes:
  - » Hybrid sound processor (CP900 series)
  - » Receiver/stimulator w/ HL24 array



# Hybrid L24 Array

- 16-mm array w/ large Stopper designed to preserve apical (low-frequency) region of cochlea



# Fitting Software

- Acoustic fitting
  - » Low-frequency audiogram
  - » Fitting prescription
  - » Compression method
  - » Split frequency for acoustic vs. electric stimulation
- Electric fitting
  - » Minimal & Maximal stimulations levels on each electrode
  - » Other electrical CI parameters

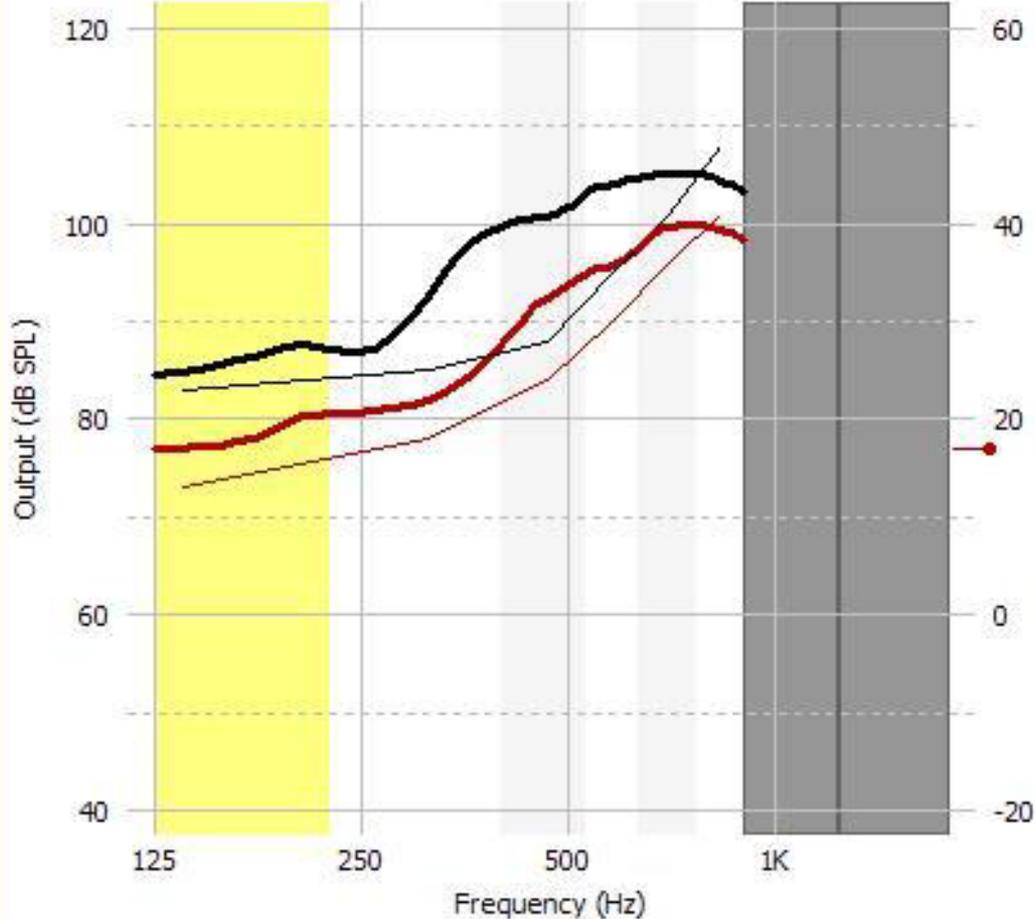


Use Acoustic Stimulation

[View Recipient's Audiogram](#)

Show 2CC values

- Target MPO
- Target Gain (60dB)
- MPO
- Aided Gain (60dB)
- Live Output



### Set Prescription

Method:  NAL-RP

WDRC  Linear

Vent Size (mm):  0

### CI Frequency Boundary

Lower:  813

### Set Gains / MPO

MPO  Gain

125Hz - 225Hz  All

2

### Miscellaneous

Delay (ms):  0

Volume Control:  Electrical only

# Preclinical Studies

- Biocompatibility
- Sterilization, packaging & shelf life
- Manufacturing processes for the implant electronics & final assembly
- Software validation
- Magnetic resonance (MR) imaging compatibility
- Electromagnetic compatibility (EMC)
- Acoustic & electrical output verification
- Hybrid L24 mechanical testing
  - » Temporal bone, mechanical, and environmental tests

# Device studied versus proposed for marketing

- Receiver/Stimulator & Array- **Identical**
- Sound processor & Fitting Software- **Modified**
  - » Specifications and bench testing show that the difference in performance between the PMA and IDE device systems is not significant

# Regulatory History

- G990155 (approved 1999)
  - » Hybrid 6: 10-mm array with 6 electrode-contacts
    - Improved speech recognition performance
    - 24/87 (28%) explanted/reimplanted
      - 2 of 24 subsequently explanted/reimplanted
- G070016 (approved April 2008)
  - » Hybrid S12: 10-mm array with 12 electrode-contacts
    - 57 subjects consented & 24 implanted
    - Improved performance at 6 months
    - 8/24 (33%) had more than 30-dB loss of residual low-frequency hearing
    - 3/24 (13%) explanted/reimplanted

## Regulatory History (cont'd)

- G070191 (approved April 2008)
  - » Hybrid L24: 16-mm array with 22 electrode-contacts
    - Pivotal IDE study for P130016
    - G070191/S026 (approved July 17, 2013)
      - Noise-reduction & environmental-classification features

# Outside U.S. studies w/ Hybrid L24

- Australian study (begun in 2005)
  - » Single site
  - » Word recognition scores improved
  - » 3/12 (25%) had threshold shifts > 30 dB
- European study (begun in 2006)
  - » 16 sites
  - » Speech recognition scores improved
  - » Group mean threshold shift of 15 dB
  - » 64/66 (97%) had round window insertion

# Regulatory History: PMAs

- P970051/S028 (approved March 2005)
  - » Nucleus 24 Cochlear Implant System
    - CI24RE receiver/stimulator
- P970051/S096 (approved August 2, 2013)
  - » Nucleus 24 Cochlear Implant System
    - CP900 sound processor w/o Acoustic Component
- P130016 (submitted May 30, 2013)
  - » Hybrid L24 (including CP900 sound processor w/ Acoustic Component)

# Rationale for Panel Meeting

- Hybrid L24: A first-of-a-kind device
  - » New proposed Indications for Use
    - Hybrid L24 candidates have significant low-frequency residual hearing unlike traditional CI candidates who have severe to profound hearing loss
  - » New technology
    - Hybrid, electric-acoustic stimulation
    - Shorter array
    - Traditional CI provides only electric stimulation via typically longer array



# Device Safety: Hybrid L24

**Anjum Khan, MD, MPH, FACS**

Medical Officer

Division of Ophthalmic and Ear, Nose and Throat Devices

FDA/CDRH/ODE

November 8, 2013

## Pivotal Study Objective

To evaluate the safety and effectiveness of the Hybrid L24 Implant System in individuals with residual low-frequency hearing (no worse than a moderate loss) and bilateral severe-to-profound high-frequency (above 1500 Hz) sensorineural hearing loss.

# Safety Endpoint

- Primary safety endpoint:
  - Defined as any surgical and /or device related event, reported as the number and proportion of individuals experiencing an adverse event
- Adverse events in the pivotal study include:
  - » Unanticipated adverse device effects
  - » Pre-specified anticipated adverse events

# Unanticipated Adverse Device Effects

- 21 CFR 812.3 (3): “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.”
- None reported by applicant

# Anticipated Adverse Events

- Sudden changes in residual low-frequency hearing
- Total loss of residual hearing
- Vertigo/dizziness (post-op) or worsened post-op
- Facial nerve problems
- Meningitis
- Perilymphatic fistulae
- Tinnitus (post-op) or worsened post-op
- Implant Migration/Extrusion
- Skin flap problems
- Device-related/programming problems

# Summary of Anticipated Adverse Events

- 65 adverse events (AE)
  - » 34/50 (68%) subjects with  $\geq 1$  AE
  - » Multiple (2-4) AEs in 19/50 (38%) subjects
- 24 of 65 AEs unresolved in 23/50 (46%) subjects



# Resolved Anticipated Adverse Events

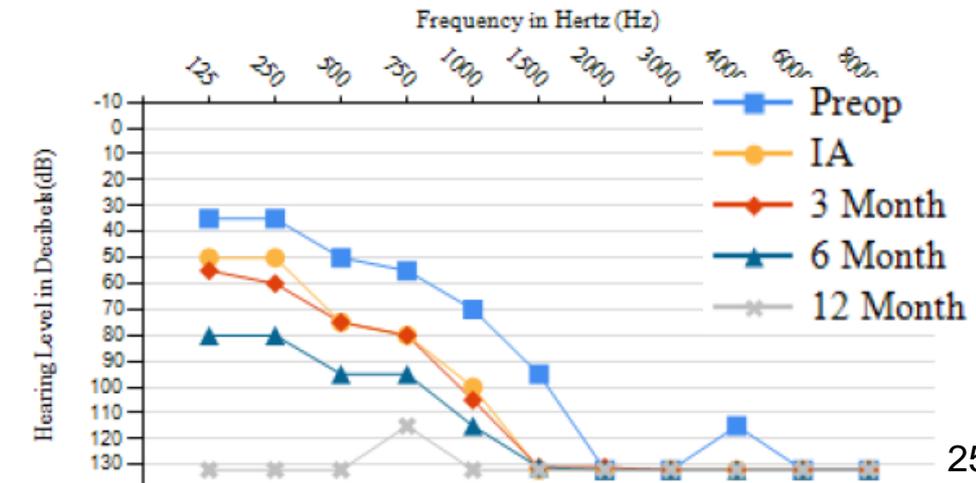
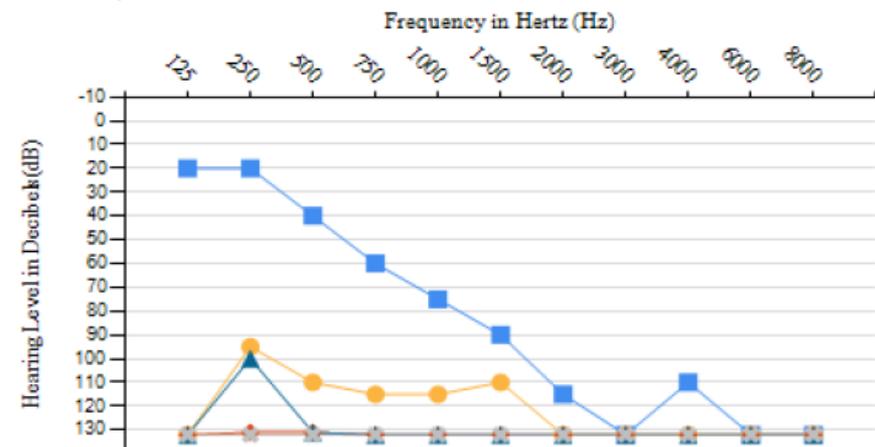
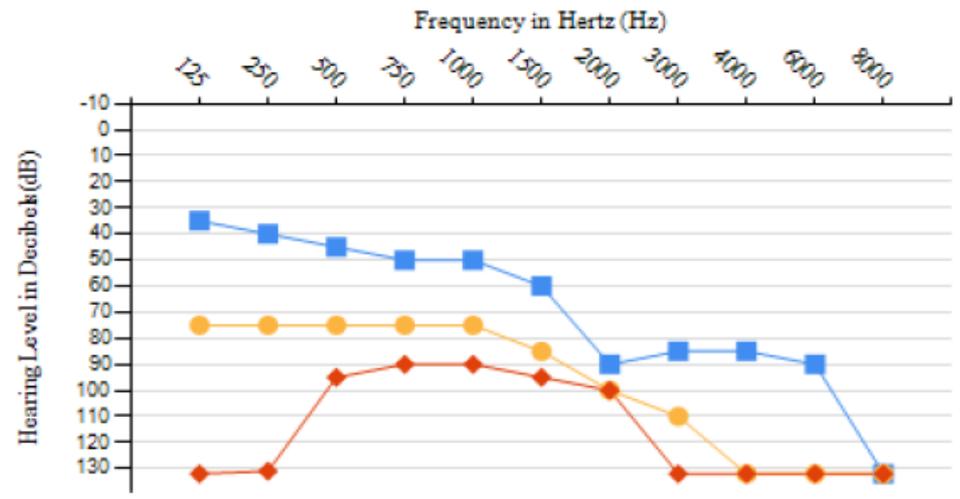
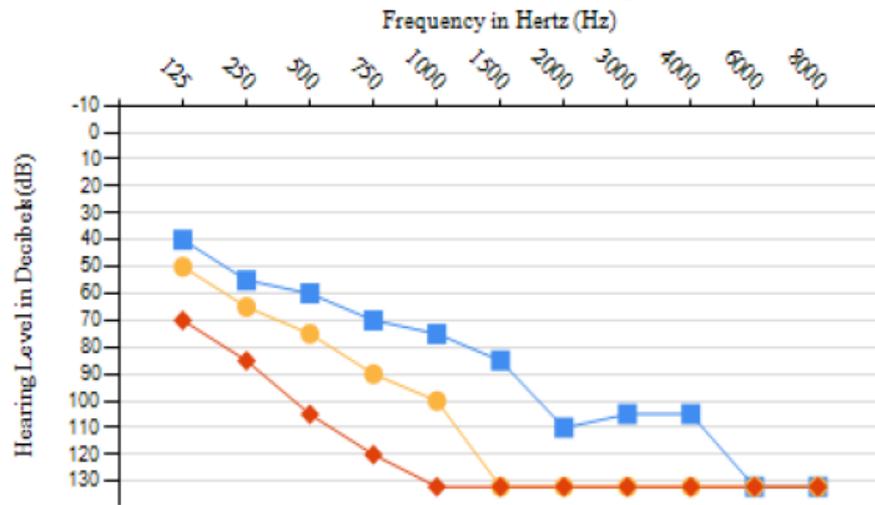
<b>Adverse Event</b>	<b>Occurring/ Resolved</b>
<b>Tinnitus (alone or with change of hearing)</b>	<b>14</b>
<b>Device related open shorts</b>	<b>11</b>
<b>Dizziness/Imbalance/Vertigo (alone or with change in hearing)</b>	<b>9</b>
2-Skin irritation, 1-Pain with MEE, 1-Local stitch infection	4
Increased impedance with change in hearing sensitivity	1
Overstimulation	1

# Unresolved Anticipated Adverse Events

Adverse Event	Occurred	Unresolved
Profound/Total loss of Hearing	22/50 (44%)	22/50 (44%)
Sound Quality Issues	2/50 (4%)	1/50 (2%)
Decreased Performance *	1/50 (2%)	1/50 (2%)

\*Explanted 8/26/13 – reported to FDA 10/24/13

# Audiograms for Explanted/Re-implanted Subjects



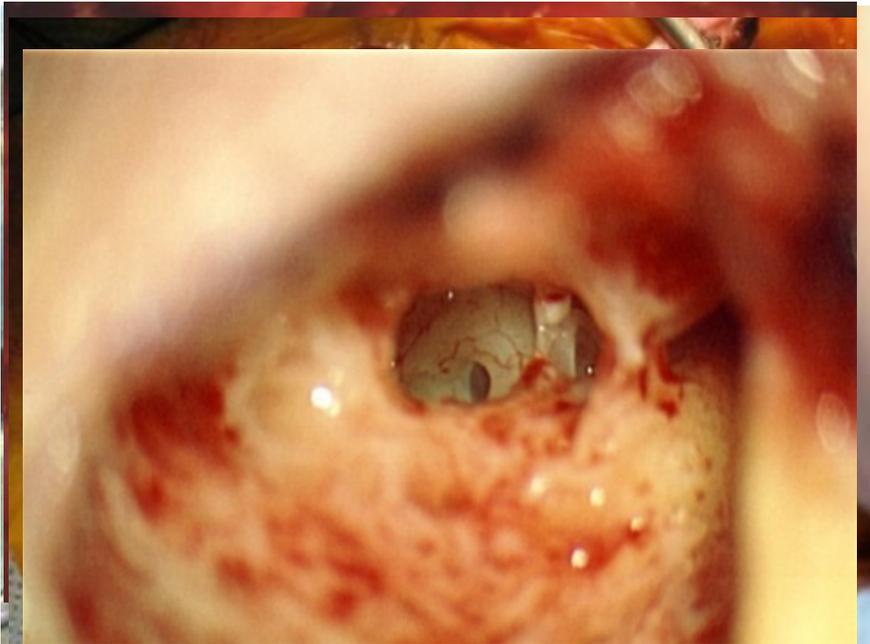
# Explanation and Re-implantation (cont'd)

- 4/50 (8%) as reported in the PMA
  - » 1 subject explanted between 3 and 6 months (partial shorts, poor performance)
  - » 1 subject between 6 and 12 months (dissatisfaction, poor performance)
  - » 2 subjects at greater than 12 months (dissatisfaction, poor performance)
  - » All reimplanted with traditional array
- 2 additional explants reported 10-24-13
  - » Updated total - 6/50 (12%)
- Future need for explantation in subjects with profound/total loss remains unknown

# Baseline Characteristics of Explanted Subjects

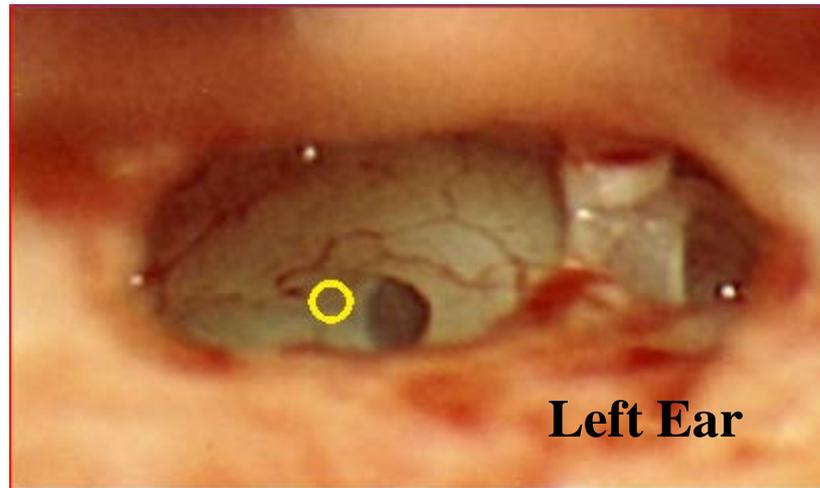
Age	Gender	Duration of Loss Prior to implantation (Years)	Etiology	Pre-op hearing threshold (dB HL)	Explant/Re-Implant Reason
67	Female	42	Unknown etiology	60	Partial shorts, poor performance
71	Male	41	Noise exposure	44	Dissatisfied
66	Male	15	Ototoxic drugs	43	Dissatisfied
81	Female	74	Familial	49	Dissatisfied
68	Male	13	Unknown etiology	47	No details provided
78	Male	38	Unknown etiology	51	Decreased performance

# Key Steps of CI Surgical Procedure



- Incision & creation of sub-periosteal pocket
- Mastoidectomy
- Well, Channel & tie downs
- Facial recess & RW verification

# Cochleostomy Insertion Technique for Hybrid L24



- A cochleostomy of 0.75mm (Yellow Circle) is made to insert the Hybrid electrode to 16mm
- In US pivotal study, placement exclusively via cochleostomy approach

# Round Window Insertion in EU Study

- In a EU study 64 of 66 implanted via round window and only 2 via cochleostomy
- Demographic and study design differences compared to the US pivotal study (e.g., gender, testing metrics, and presentation levels)
- Difficult to evaluate the impact of insertion technique on outcome based on difference between the US and EU studies

## Panel Question

In the proposed labeling, the applicant states that the Hybrid L24 electrode may be inserted either via a cochleostomy or the round window. However, all cases in the pivotal clinical study were inserted via cochleostomy. In a European study conducted using the Hybrid L24 implant, 64 of 66 subjects were implanted using the round window approach. Any comparison between the US pivotal and the European study to assess impact of the surgical approach on the safety and effectiveness of the Hybrid L24 implant is limited due to differences in study populations and study design. Please discuss whether the currently available information supports labeling the Hybrid L24 implant for both the cochleostomy and the round window approach.

# Clinical Audiology Review

## Nucleus<sup>®</sup> Hybrid<sup>™</sup> L24 Implant System

**Shu-Chen Peng, Ph.D., CCC-A**

Clinical Audiology Reviewer

Division of Ophthalmic and Ear, Nose and Throat Devices

FDA/CDRH/ODE

November 8, 2013

# Outline

- Pivotal Study Overview
- Clinical Study Population & Subject Accountability
- Study Outcomes
  - » Changes in amounts of hearing and hearing sensitivity
  - » Device effectiveness
- Additional Analyses and Effectiveness Measures

# Pivotal Study Overview

- Non-blinded, single-arm study design
- Repeated measures, within-subject control
  - » Commonly accepted design for IDE studies with implantable auditory prostheses
  - » Addressing large individual variability among subjects with HL, reducing treatment-effect variance

# Subject Accountability

100 subjects consented:

- 50 implanted
- 50 not implanted
  - » 22 not meeting study candidacy requirements
  - » 28 potential candidates:
    - Insurance issues (n = 16)
    - Pursuing other options (n = 8)
      - Hearing aid amplification (n = 3)
      - No longer interested / concerns regarding loss of residual hearing (n = 3)
      - Traditional CI (n = 2)
    - Maximum number of subjects reached (n = 4)

## Key Inclusion Criteria

- **18 years of age or older** at time of implantation
- Severe to profound SNHL at frequencies  
> 1500 Hz
- Low-frequency thresholds < 60 dB HL
- Aided CNC Words:
  - » Implanted ear:
    - $10\% \leq \text{score} \leq 60\%$
  - » Contralateral ear:
    - score < 80%
    - $\geq$  score in implanted ear

# Subject Demographics

Of the 50 implanted subjects:

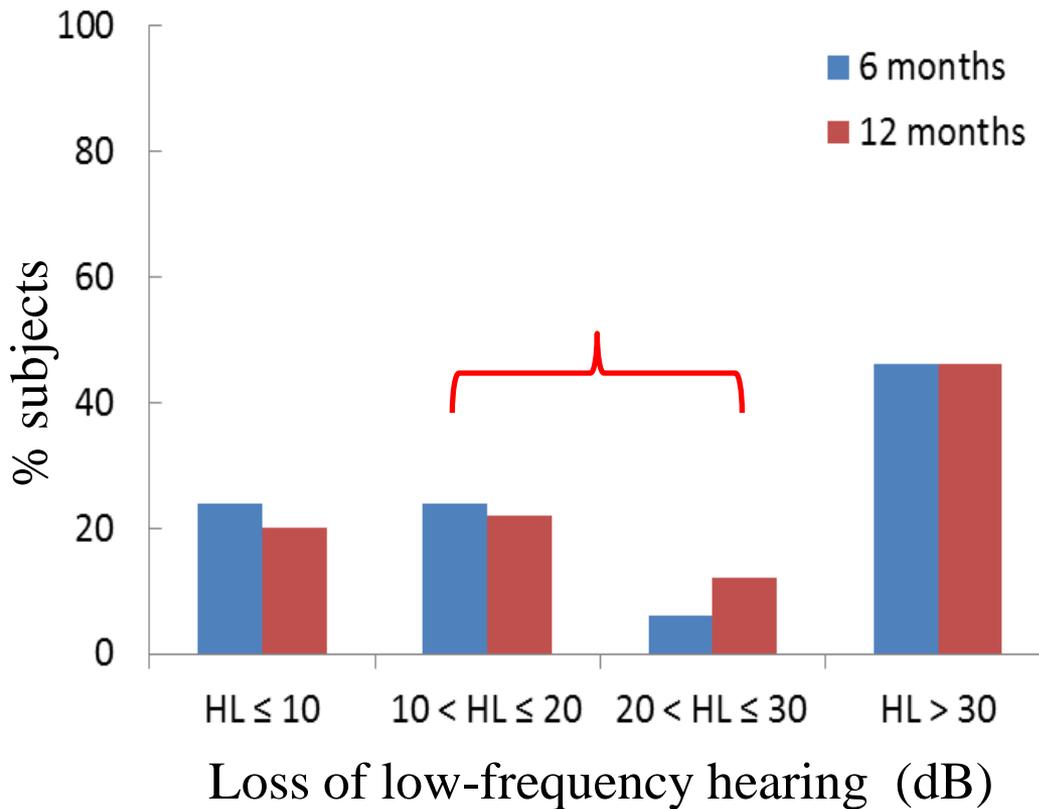
- Age: **23** – 86.2 years
  - » One subject aged 23
  - » Remaining subjects aged  $\geq 37$
- Gender: Equal between male and female
- Duration of HL: 3.4 – 73.9 years
- Duration of severe-profound high-frequency HL: 1.6 – 30.1 years

# Question for Panel Discussion

The clinical cohort primarily consisted of subjects aged 37 years and older (only one subject was age 23 years old). The applicant proposes a minimum of 18 years for the indicated patient population. FDA regulations for medical devices consider the age group of 18 through 21 years as “transitional adolescents” and include this group in the pediatric population (21 years old or younger).

Please discuss whether there is sufficient information to extrapolate the use of this device to patients 18 years and older. In your discussion please consider factors such as psychological competence, neurocognitive development, and the presence of congenital syndromes for the transitional adolescent population.

# Low-frequency Hearing Loss: FDA Analysis

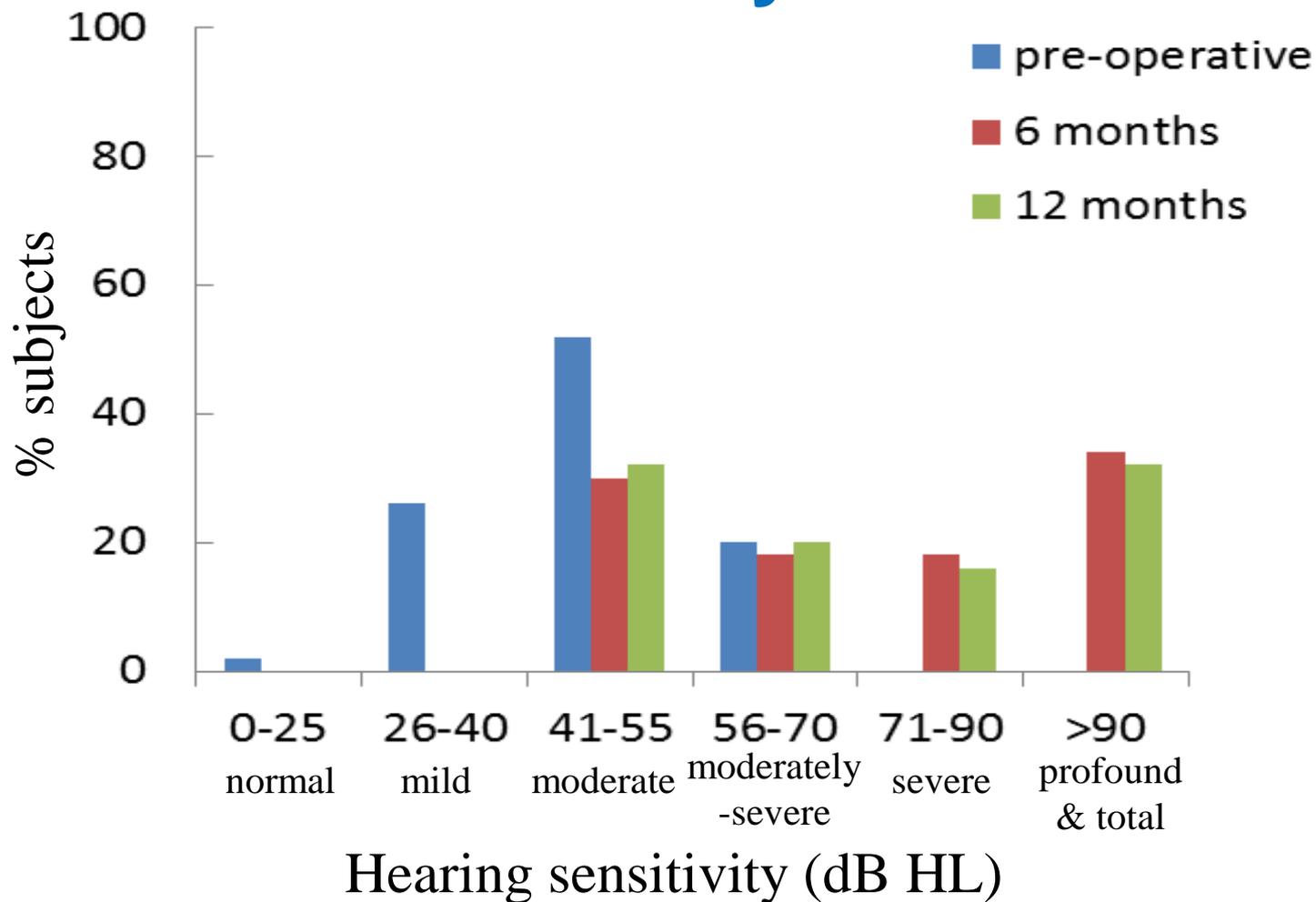


- At 6 months:
  - » >30 dB: 23/50 (**46%**)
  - » 10 < HL ≤ 30 dB: **15/50 (30%)**
- At 12 months:
  - » >30 dB: 23/50 (**46%**)
  - » 10 < HL ≤ 30 dB: **17/50 (34%)**

## Question for Panel Discussion

In the PMA, the applicant states that threshold changes  $\leq 30$  dB are “unlikely to impact functional low-frequency hearing” and changes  $> 30$  dB are “likely to impact functional low-frequency hearing.” Please discuss the clinical significance of the residual low-frequency hearing loss between 10 and 30 dB experienced by 30% (15 of 50) of the subjects at 6 months.

# Low-frequency Hearing Sensitivity: FDA Analysis



# Profound/Total Hearing Loss: FDA Analysis

- 17/50 (34%): At 6 months
- 5 additional subjects at 12 months or later:
  - » 1 at 12 months
  - » 2 at 18 months
  - » 1 at 36 months
  - » 1 at 48 months

# Question for Panel Discussion

The pivotal study results indicate that 34% (17 of 50) of subjects' residual hearing sensitivity is at the profound/total hearing loss levels at the 6-month interval. Among the subjects who had data available beyond the 6-month interval, 5 developed profound/total hearing loss at a later interval (one at 12 months, two at 18 months, one at 36 months, and one at 48 months). Please discuss the following:

- (a) The clinical significance of this residual low-frequency hearing loss at the 6- and 12-month intervals, and
- (b) Whether the limited long-term residual hearing loss data raise safety concerns for the Hybrid L24 implant system.

## Question for Panel Discussion

The proposed Indications for Use does not specify any requirement for a trial of appropriately fit hearing aids. However, 3 subject candidates underwent the trial of appropriately fit hearing aids as part of the study requirements decided to pursue hearing aid amplification in lieu of the Hybrid L24. Given the high incidence of profound or total loss of residual low frequency hearing (22/50 subjects, 44%), please comment on the appropriateness of requiring a hearing aid trial with properly fit hearing aids. If you believe such a criterion is necessary, please also comment on the minimum length of such a hearing aid trial prior to implantation.

# Co-Primary Effectiveness Endpoints

- Test Metrics
  - » CNC Word Recognition Test
  - » AzBio Sentence-in-Noise Test
- Test Conditions to be Compared
  - » Preoperative baseline – Acoustic Alone in ear to be implanted
  - » At 6 months – Hybrid Alone in implanted ear

# Co-primary Endpoints at 6 Months: FDA Analysis

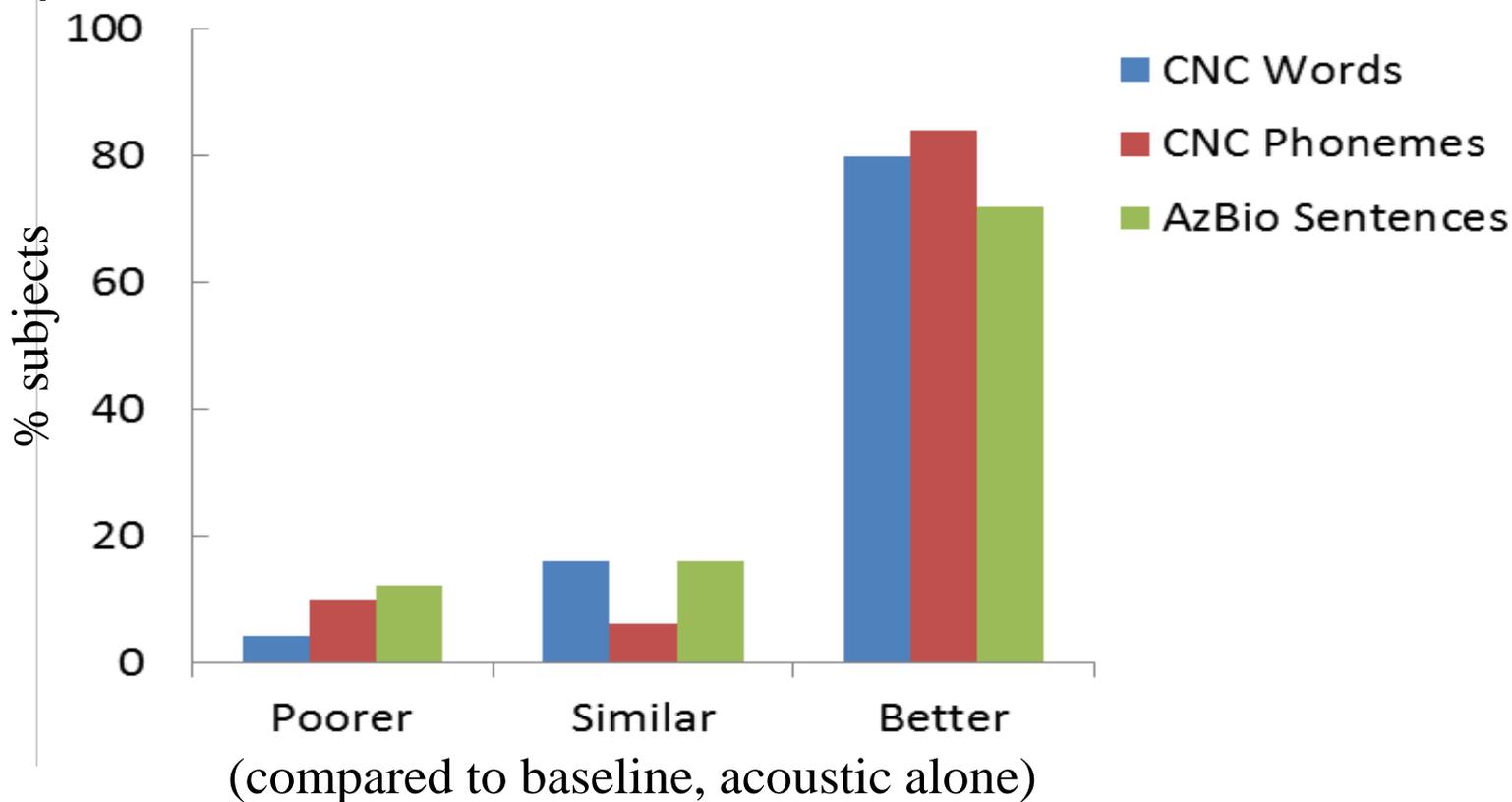
	<b>Mean ± SD at baseline (%)</b>	<b>Mean ± SD 6 months (%)</b>	<b>Change (endpoint) (%)</b>
CNC Words	28.4 ± 14.7	64.2 ± 26.6	35.8 ± 27.7
AzBio	16.3 ± 14.4	48.3 ± 31.3	32.0 ± 29.4

# Secondary Effectiveness Endpoints

- Test scores
  - » CNC Words
  - » CNC Phonemes
  - » AzBio Sentences
- Test Conditions to be Compared
  - » Preoperative baseline – Acoustic Alone in ear to be implanted
  - » At 6 months – Hybrid Alone in implanted ear
- For each score, endpoint would be achieved if > 75% subjects scored similar or better

# Secondary Effectiveness Outcomes: FDA Analysis

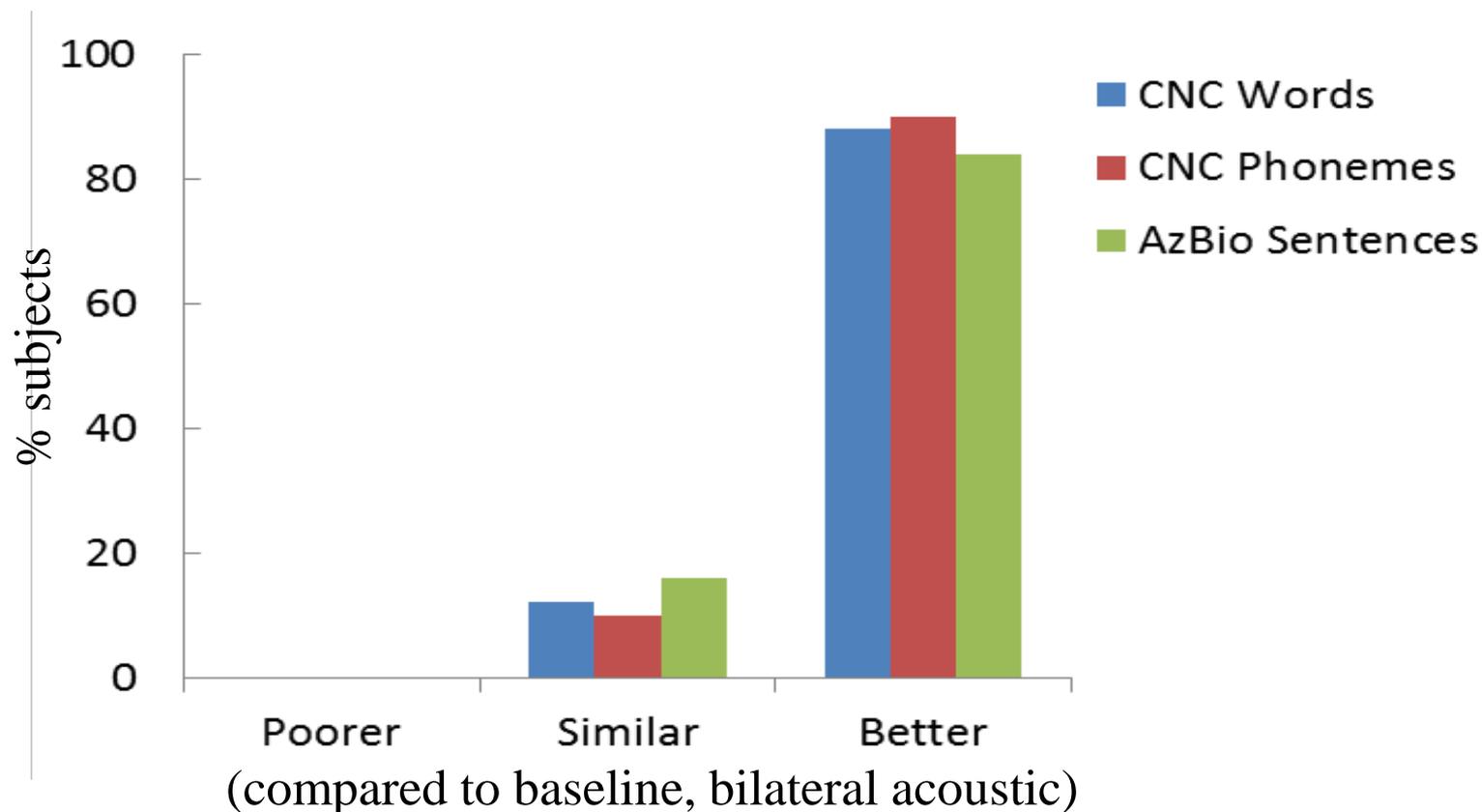
- Hybrid Alone vs. pre-implant Acoustic Alone performance at 6 months:



# Combined Test Condition

- Hybrid L24 used in conjunction with acoustic hearing in the contralateral ear
  - » Test Metrics
    - CNC Word Recognition Test
    - AzBio Sentence-in-Noise Test
  - » Test Conditions to be Compared
    - Preoperative baseline – Bilateral Acoustic
    - At 6 months – Combined

# Effectiveness Outcomes in Combined Condition: FDA Analysis



## Question for Panel Discussion

The proposed Indications for Use does not explicitly specify unilateral implantation. All subjects in the pivotal clinical study were implanted unilaterally with the Hybrid L24 device. In the Hybrid test condition, a small portion of study subjects performed poorer for CNC Words (4.0%), CNC Phonemes (10.0%), and the AzBio Sentences in Noise (12.0%), as compared to their pre-operative performance. In the Combined test condition, where the subjects used their contralateral residual low-frequency hearing, all subjects performed equal or better on these assessments. Please discuss whether the Hybrid L24 should be explicitly indicated for only unilateral implantation to reduce the possibility of residual low-frequency hearing loss in the contralateral ear.

# Additional Effectiveness Measures: Speech and Music Perception

- Speech Reception Threshold (SRT) in Noise Test
  - » Performed in only 35/50 subjects
- The University of Washington Clinical Assessment of Music Perception (UW-CAMP)
  - » 3 subtests
  - » Measured in Hybrid and Combined conditions, preoperatively and at the 6-month interval
  - » Performance not significantly different between preoperative baseline and at 6 months (unilateral or bilateral)

# Additional Effectiveness Measures: Patient-Reported Outcomes

- Questionnaires Used
  - » The Speech, Spatial and Sound Qualities Questionnaire (SSQ)
  - » Device Use Questionnaire (DUQ)
  - » Musical Background Questionnaires (MBQ)
- Limitations
  - » Lack of control group or blinding (subjective)
  - » Insufficient psychometric validations

*Patient Reported Outcome Measures Labeling Guidance (2009)*

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm193282.pdf>

# **Statistical Considerations in PMA P130016 Nucleus<sup>®</sup> Hybrid<sup>™</sup> L24 Implant System**

**Nelson Lu, Ph.D.**

Statistician

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Office of Surveillance and Biometrics

FDA/CDRH

November 8, 2013

# Co-Primary Effectiveness Endpoints

- Test Metrics
  - » CNC word recognition test
  - » AzBio sentence test in noise
- Test Conditions to be Compared
  - » Preoperation – Acoustic alone in ear to be implanted
  - » 6-month postactivation – Hybrid mode in treated ear

# Co-Primary Effectiveness Endpoints (cont'd)

- Hypothesis

$$H_0: \mu_D \leq 0$$

$$H_A: \mu_D > 0$$

$\mu_D$ : mean difference between 6-month and pre-operative scores

- Test methods, using 1-sided  $\alpha = 0.025$

- » Normality assumption hold  $\rightarrow t$ -test

- » Normality assumption not hold  $\rightarrow$  Wilcoxon signed rank test

# Co-Primary Effectiveness Endpoints Results

	<b>Baseline Mean ± SD</b>	<b>6 Month Mean ± SD</b>	<b>Change Mean ± SD</b>	<b>95% CI</b>	<b>p-value</b>
<b>CNC Words</b>	28.4 ± 14.9	65.4 ± 25.4	37.0 ± 26.6	(29.4, 44.6)	< 0.0001
<b>AzBio</b>	16.4 ± 14.5	49.2 ± 30.8	32.8 ± 29.1	(24.5, 41.2)	< 0.0001

Based on 49/50 (98%) subjects who completed 6-month effectiveness evaluation

# Co-Primary Effectiveness Endpoints: Missing Data (1 Subject)

Observed

	<b>Pre-op</b>	<b>3 months</b>	<b>Change</b>
<b>CNC Words (%)</b>	27	3	-24
<b>AzBio (%)</b>	9.7	1.4	-8.3

Imputation on change at 6-month

	<b>LOCF</b>	<b>Worst Case</b>
<b>CNC Words (%)</b>	-24	-27
<b>AzBio (%)</b>	-8.3	-9.7

# Co-Primary Effectiveness Endpoints Results

	LOCF		Worst Case	
	Change (95% CI )	P-value	Change (95% CI )	P-value
<b>CNC Words (%)</b>	35.8 (27.9, 43.8)	< 0.0001	35.7 (27.8, 43.6)	< 0.0001
<b>AzBio (%)</b>	32.0 (23.7, 40.4)	< 0.0001	32.0 (23.6, 40.4)	< 0.0001

# Covariate Analysis

- Baseline covariates
  - » Gender
  - » Age at implantation (years)
  - » Duration of hearing loss (years)
  - » Duration of severe or profound high-frequency hearing loss (years)
  - » Preoperative CNC scores (%)
  - » Preoperative low frequency hearing threshold (dB HL)
- Multivariate linear regression of each primary effectiveness endpoint using all 6 variables

# Covariate Analysis Results

- Significant covariates

	CNC Improvement		AzBio Improvement	
	Estimate (%)	p-value	Estimate (%)	p-value
<b>Duration of HL (years)</b>	-0.54	0.04	-0.63	0.04
<b>Pre-op LF hearing (dB HL)</b>	-0.84	0.02	-1.08	0.01

- Shorter duration of hearing loss and/or better pre-operative hearing threshold may be associated with better effectiveness performance.

# Applicant's Classification of Hearing Sensitivity

- Dichotomized into two groups:
  - » Group 1: LF hearing sensitivity  $\leq 90$  dB HL
  - » Group 2: LF hearing sensitivity  $> 90$  dB HL

# Hearing Assessment for Safety: Missing Data (2 Subjects)

- One reimplanted with a traditional CI before 6 months
  - » at 3 months: 102.4 dB HL
- One with no available audiometric data (later reimplanted with a traditional CI)
  - » at 3 months: 107.6 dB HL
- Both counted as Group 2 subjects

# Improvement in CNC Words: Group 1 vs. Group 2

- Mean (SD)
  - » Group 1: 46.9% (20.2%)
  - » Group 2: 14.2% (28.0%)

	<b>Poorer</b>	<b>Similar</b>	<b>Better</b>
<b>Group 1</b>	0/33 (0%)	1/33 (3%)	32/33 (97%)
<b>Group 2</b>	2/17 (12%)	7/17 (41%)	8/17 (47%)

# Improvement in AzBio: Group 1 vs. Group 2

- Mean (SD)
  - » Group 1: 44.9% (24.0%)
  - » Group 2: 7.0% (22.0%)

	<b>Poorer</b>	<b>Similar</b>	<b>Better</b>
<b>Group 1</b>	0/33 (0%)	2/33 (6%)	31/33 (94%)
<b>Group 2</b>	6/17 (35%)	6/17 (35%)	5/17 (30%)

## CNC by AzBio Results: Group 1 vs. Group 2

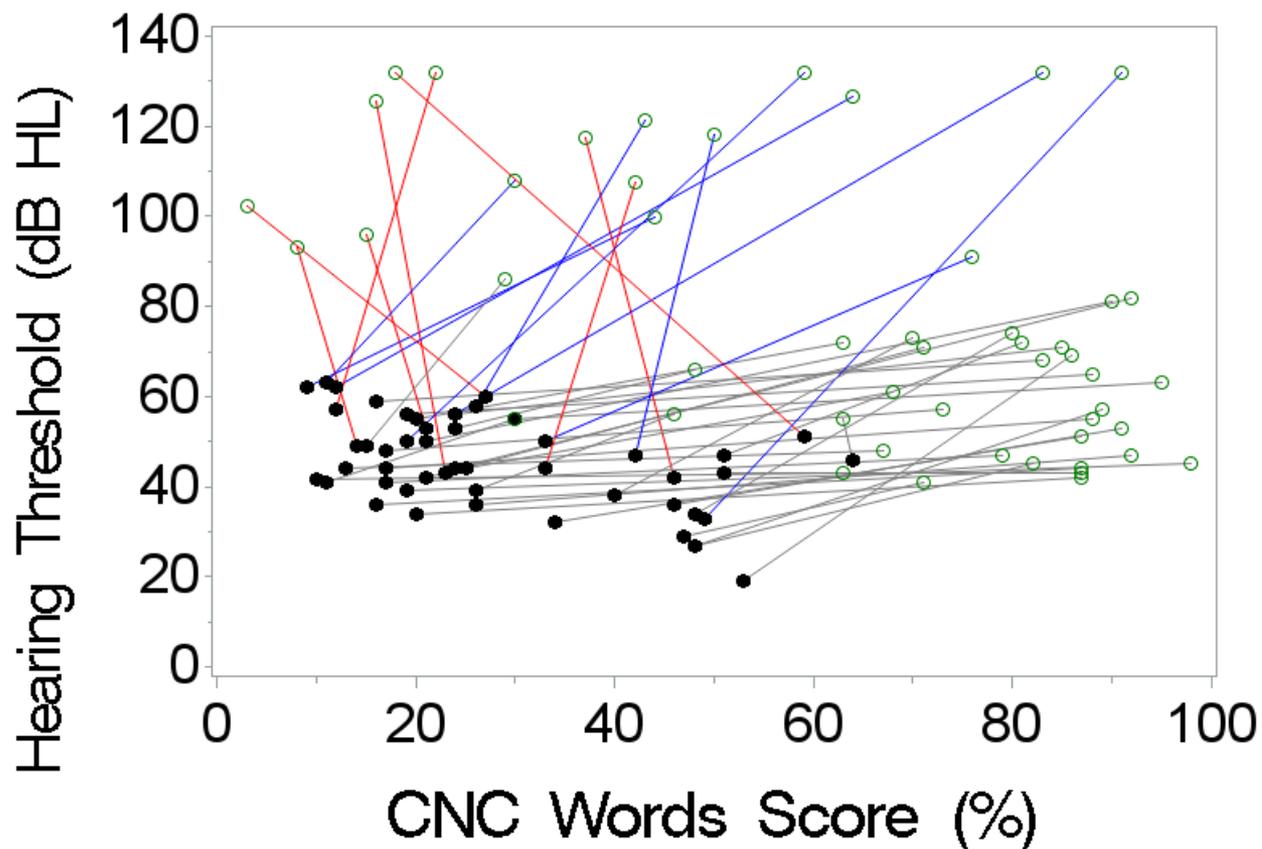
- Group 1: 33/33 improved in at least one tests.
- Group 2: 8/17 did not improve in either test.
  - » 2: poorer AzBio; poorer CNC
  - » 3: poorer AzBio; similar CNC
  - » 3: similar AzBio; similar CNC

# Device Benefit vs. Residual Hearing Preservation (6 mo)

	<b>Benefit</b>	<b>Proportion</b>
<b>Group 1</b> ( $\leq 90$ dB HL)	Yes	33/50 (66%)
<b>Group 2</b> ( $> 90$ dB HL)	Yes	9/50 (18%)
	No	8/50 (16%)

\* Benefit: Improvement in at least one speech test

# Change in Hearing Threshold vs. Change in CNC Words



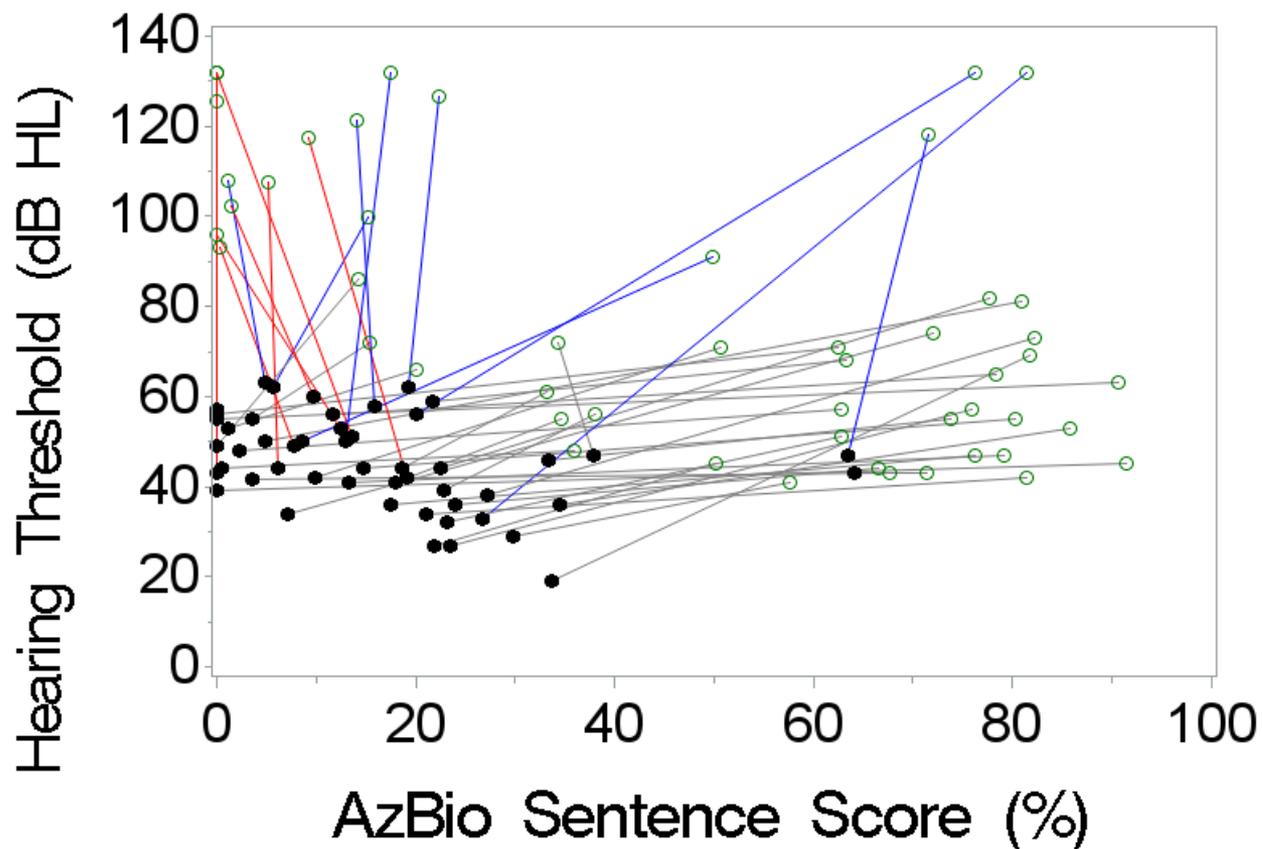
Grey: Group 1

Blue: Group 2, benefit

Red: Group 2, no benefit

••• Pre-op    ○○ 6-month

# Change in Hearing Threshold vs. Change in AzBio Sentence



Grey: Group 1

Blue: Group 2, benefit

Red: Group 2, no benefit

••• Pre-op    ○○ 6-month

# Poor Performer vs. 6 Baseline Covariates

- Using multivariate logistic regression
- Significant factor: Duration of hearing loss
  - » Odds ratio (5-year increment) = 1.61;  $p=0.03$
- Odds of being a poor performer may increase with longer duration of hearing loss.

## Question for Panel Discussion

The pivotal study reveals that 34% (17 of 50) of subjects who received a Hybrid L24 implant exhibited a profound loss (90+ dB HL) or total loss (no measurable hearing) for their residual low-frequency hearing at the 6-month interval following implantation. As part of the analyses of the pivotal study data, the applicant analyzes effectiveness data based on the dichotomization of the subjects' status of residual low-frequency hearing sensitivity – Group 1 has subjects whose hearing loss is in the range of severe or better (moderate, moderately-severe, and severe), while Group 2 has subjects whose hearing loss is in the range of profound (profound and total). Please discuss the appropriateness of the applicant's classification and analysis of hearing loss data which they use to characterize the clinical significance of residual hearing losses observed in the study.



# Post-Approval Study (PAS) Considerations

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## Reminder

- The discussion of a PAS prior to FDA determination of device approvability should not be interpreted to mean FDA is suggesting that the device is safe and effective.
- The plan to conduct a PAS does not decrease the threshold of evidence required by FDA for device approval.
- The premarket data submitted to the Agency and discussed today must stand on their own in demonstrating a reasonable assurance of safety and effectiveness and an appropriate benefit/risk balance.

# General Principles for Post-Approval Studies

- Objective is to evaluate device performance and potential device-related problems in a broader population and/or over an extended period of time after premarket establishment of reasonable evidence of device safety and effectiveness
- Post-approval studies should not be used to evaluate unresolved issues from the premarket phase that are important to the initial establishment of device safety and effectiveness

# Important Postmarket Issues

- What is the longer term performance of the device?
  - » Long-term data on device safety and effectiveness
- What is the real world experience with the device?
  - » Broader patient population
- Novel, collaborative approach for postmarket evaluation
  - » IDE/PAS cohort

# Applicant's Postmarket Proposal

The applicant is proposing to conduct two post approval studies for the current PMA:

- Extended Follow-up of the Premarket cohort (5 years post-activation)
- New Enrollment Study (3-years post-activation)

# Applicant's Proposed PAS Outline – Extended Follow-up of the Premarket Cohort

<b>Study Design</b>	Prospective, multicenter, single arm study
<b>Study Population</b>	Existing premarket cohort who will agree to participate in an evaluation of the <u>next generation CP900 processor with new, investigational features.</u>
<b>Sample Size</b>	Up to 47 subjects*
<b>Length of follow up</b>	Annual visits for 5 years after device activation

# Applicant's Proposed PAS Outline – Extended Follow-up of the Premarket Cohort

<b>Safety Endpoint</b>	Type and frequency of adverse events and serious adverse events
<b>Effectiveness Endpoint</b>	<ul style="list-style-type: none"> <li>- Consonant Nucleus Consonant (CNC) test</li> <li>- AzBio test</li> </ul>
<b>Statistical Plan</b>	<ul style="list-style-type: none"> <li>- Adverse events rates will be compared to pivotal study               <ul style="list-style-type: none"> <li>- Frequency of AEs (95% CI)</li> <li>- Number of events per patient-time</li> </ul> </li> <li>- Mean differences in CNC and AzBio scores analyzed using paired t-tests (pre-operative vs 60 months)</li> </ul>

# FDA Assessment of Proposed Extended Follow-up PAS

- Novel approach for a PAS
  - » Existing premarket cohort who agree to participate in a new IDE study to evaluate the new investigational features of CP900 series
  - » On/off function of investigational features may allow same study cohort to be used for an IDE and a PAS
- Potential challenges in assessment of device effectiveness
  - » Methodology of the assessment
  - » Potential carry-over effect

# Questions for Panel Discussion

## Extended Follow-up of Premarket Cohort

- a. Please discuss the appropriateness of this study population (existing premarket cohort who agree to participate in an IDE study to evaluate the new investigational features of the CP900 series) to evaluate the long-term safety and effectiveness of the Hybrid L24 Implant System, with specific considerations of the audiological measurements and a potential carry-over effect due to the on/off function of investigational features.
- b. The applicant has proposed that the device effectiveness will be assessed by comparing within-subject differences measured by CNC and AzBio tests between the preoperative and 60 months post-activation interval. Considering the proposed study population, please discuss how device effectiveness should be measured in this study.

# Questions for Panel Discussion

- c. The applicant has proposed to continue to follow the subjects for 5 years post-activation of the device. Please discuss the appropriate duration for this study.

# Applicant's Proposed PAS Outline – New Enrollment Study

<b>Study Design</b>	Prospective, multi-center, single arm study
<b>Study Population</b>	Minimum of 50 newly enrolled subjects
<b>Sample Size</b>	Up to 25 sites
<b>Length of follow up</b>	Baseline, initial device activation, and 6, 12, 24 and 36 months post-activation

# Applicant's Proposed PAS Outline – New Enrollment Study (*continued*)

<p><b>Safety Endpoint</b></p>	<p>Type and frequency of adverse events and serious adverse events</p>
<p><b>Effectiveness Endpoint</b></p>	<ul style="list-style-type: none"> <li>• Consonant-Nucleus- Consonant (CNC) test</li> <li>• AzBio test</li> </ul>
<p><b>Statistical Plan</b></p>	<ul style="list-style-type: none"> <li>• Adverse events rates will be compared to pivotal study             <ul style="list-style-type: none"> <li>» Frequency of AEs (95% CI)</li> <li>» Number of events per patient-time</li> </ul> </li> <li>• Mean differences in CNC and AzBio scores analyzed using paired t-tests (pre-operative vs 36 months)</li> </ul>

# FDA Assessment of Proposed New Enrollment PAS

- Effectiveness- within-subject differences, CNC and AzBio tests
  - » Additional long term effectiveness endpoints
- Modified device use questionnaire (DUQ) and health utility index (HUI) questionnaire
  - » DUQ is not a validated instrument
  - » HUI is a generic instrument
- Duration of follow-up 3 years

# Questions for Panel Discussion

## New Enrollment Study

- a. The applicant plans to assess device effectiveness by comparing within subject differences measured by CNC and AzBio tests between pre-operative and 36 months. Please discuss if there are any additional long term effectiveness endpoints that should be evaluated in the postmarket setting.
  
- b. The applicant has proposed to collect data on patient reported outcomes by administering a modified device use questionnaire (DUQ) and health utility index (HUI) questionnaire. Please discuss if there are any other additional patient reported outcomes to be evaluated.

## Questions for Panel Discussion

- c. The applicant has proposed to follow the subjects for 3 years post-activation of the device. Please discuss the appropriate duration for this study.
  
- d. Please discuss if there are any additional considerations that need to be taken into account for the new enrollment study.



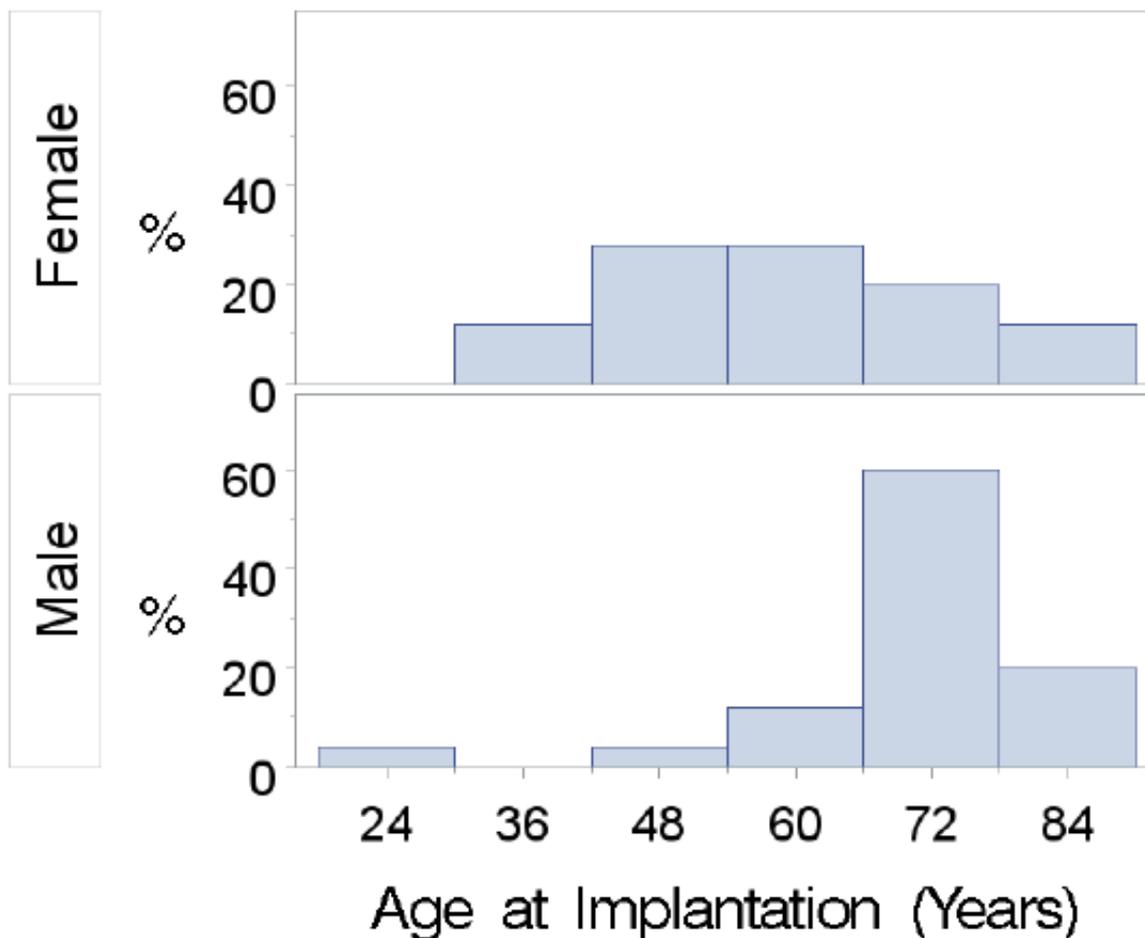
# Presented Backup Slides

# Information for Explanted Subjects

- 5/6 lost residual hearing and had not improved in either of the 2 tests at 6 months
- 1/6 lost the residual hearing before 3 months and had some benefit at 6 and 12 months

CNC Words (%)			AzBio Sentences (%)		
Pre-op	6 mo	12 mo	Pre-op	6 mo	12 mo
42	50	84	63.5	71.6	86.1

# Distribution of Age at Implantation



## Relationship: Group 2 and Baseline Covariates

- Multivariate logistic regression of profound/total hearing loss using 6 baseline covariates
- Significant factors:

	Odds Ratio	p-value
<b>Pre-op LF hearing (+5 dB HL)</b>	2.4	0.002
<b>Gender (M vs. F)</b>	6.1	0.045

- » Odds of developing profound/total hearing loss may increase with poorer pre-op hearing threshold
- » Male may have higher odds in developing profound/total hearing loss