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Cochlear Americas

The Nucleus® Hybrid™ L24 Implant System: New Enrollment Study

P130016/S003

Statistical Analysis Plan

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Version 5.0

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1. Purpose

This statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analysis of data collected under the Cochlear Americas, Post Approval Study: The Nucleus® Hybrid™ L24 Implant System New Enrollment Study protocol.

2. Scope

This SAP should be read in conjunction with the study protocol. This version of the plan has been developed with respect to the CAM-5573-HYB-PMA protocol version 8, dated April 2022. Any further changes to the protocol may necessitate updates to the SAP.

3. Applicable Documents

Document Number	Document Title
CAM-5573-HYB-PMA	The Nucleus® Hybrid™ L24 Cochlear Implant System: New Enrollment Study

4. Software

All tables, listings and figures will be produced using SAS Version 9.3 or higher (SAS Institute, Cary, NC.) or another validated statistical software package.

5. Definitions

AE	-	Adverse Event
ANOVA	-	Analysis of Variance
AzBio Test	-	A sentence level speech recognition test delivered in background noise at a predetermined signal to noise ratio
Bimodal Mode	-	Use of acoustic hearing, with or without amplification, in addition to electric hearing via a cochlear implant or Hybrid implant in the contralateral (opposite) ear
CMH	-	Cochran–Mantel–Haenszel test
CNC Test	-	Consonant-Nucleus-Consonant Test: A monosyllabic word-level test given in quiet and calculated both as a word correct score and a phoneme correct score
Combined Mode	-	Use of acoustic hearing bilaterally, with or without amplification, in addition to electric hearing via a cochlear implant or Hybrid L24 implant
eCRF	-	Electronic Case Report Form
DUQ	-	Device Use Questionnaire: "In-house" device usability metric, administered to determine subjective preference and satisfaction with regards to device use in various listening environments
Enrolled	-	Subjects will be enrolled in the study once the inclusion/exclusion criteria are met
Everyday Listening Condition	-	Postoperative listening condition referring to either Combined Mode or Bimodal Mode
HUI	-	Health Utility Index
Hybrid Mode	-	Combination of acoustic and electric hearing in the same ear
ICF	-	Informed Consent Form
ITT	-	Intent-to-Treat

PTA	-	Pure tone audiometry
QOL	-	Quality of Life
SAE	-	Serious Adverse Event
Screened	-	Each subject who signs the study ICF will be considered a screened subject.
SNR	-	Signal-to-Noise Ratio
SSQ	-	Speech, Spatial, and Qualities of Hearing Scale: validated metric used as a self-assessment of hearing in everyday life across three hearing domains: speech hearing, spatial hearing, and qualities of sound
UADE	-	Unanticipated Adverse Device Effect
VAS	-	Visual Analog Scale

6. Trial Design

The Nucleus® Hybrid™ L24 Cochlear Implant System New Enrollment Post Approval Study is a prospective, multicenter, single-arm, open label clinical trial. There will be up to 25 investigational centers enrolling a minimum of 50 newly implanted subjects aged 18 years or older at the time of implant.

Upon baseline evaluation, subjects are scheduled for device implantation. To allow for healing, initial activation will occur approximately 3-5 weeks post-surgery. Key evaluations will be recorded at 3 months, 6 months, and 12 months. Annual evaluations will be carried out thereafter to 3 years postactivation.

Evaluable subjects will undergo a preoperative candidacy assessment and baseline evaluation to determine study eligibility. Subjects will be implanted with the device and initial activation will occur approximately 3-5 weeks post-surgery. The result of this design will be that the trial will allow for assessment of the within-subject effect of receiving the Nucleus® Hybrid™ L24 Cochlear Implant compared to baseline.

Subjects will not be blinded as it is not possible to conceal the presence or absence of an implant from a recipient and/or clinical investigators. To minimize order effects and test bias at each evaluation, sentence lists assigned to the various test conditions will be randomized across conditions, and the order in which test conditions are completed will be randomized.

Schedule of procedures:

Follow-up visit	Test and Procedure
Initial activation: 3-5 weeks post-surgery	• Otologic & Medical History • Unaided Audiometric Thresholds • Tympanometry • Aided Audiometric Thresholds • External Equipment Check
3 months	• Otologic & Medical History • Unaided Hearing Thresholds • Aided Audiometric Thresholds • External Equipment Check • CNC test (implant ear and both ears) • AzBio +5dB and/or +10dB SNR (Implant Ear Hybrid mode, Implant Ear Electric Only & Both Ears)
6 months	• Otologic & Medical History • Unaided Hearing Thresholds • Aided Audiometric Thresholds • External Equipment Check • CNC test (implant ear and both ears) • AzBio-+5dB and/or +10dB SNR (Implant Ear Hybrid mode, Implant Ear Electric Only & Both Ears) • DUQ • SSQ • HUI • Hybrid Post Market Cost of Ownership Survey
12 months	• Otologic & Medical History • Unaided Hearing Thresholds • Aided Audiometric Thresholds • External Equipment Check • CNC test (implant ear and both ears) • AzBio-+5dB and/or +10dB SNR (Implant Ear Hybrid mode, Implant Ear Electric Only & Both Ears) • DUQ • SSQ • HUI • Hybrid Post Market Cost of Ownership Survey
2 years and annually through 3 years	• Otologic & Medical History • Unaided Hearing Thresholds • Aided Audiometric Thresholds • External Equipment Check • CNC test (implant ear and both ears) • AzBio-+5dB and/or +10dB SNR (Implant Ear Hybrid mode, Implant Ear Electric Only & Both Ears) • SSQ

Additional data for analysis will come from subjects in the Hybrid Extended Duration Study as well as real world evidence (RWE) from a retrospective study of patients [redacted] Data from the Hybrid Extended Duration study will be pooled with the New Enrollment study for analysis of effectiveness. Data from both the Hybrid Extended Duration study and the RWE study [redacted] will be pooled with the New Enrollment study for analysis of safety.

7. Trial Objectives

The purpose of this trial is to evaluate the long term safety and effectiveness of the Nucleus® Hybrid L24 Cochlear Implant System (Cochlear Americas, Centennial CO USA) in a newly implanted population for 3 years.

The study will also allow for the evaluation of training programs and further exploration of the type and frequency of adverse events beyond that which could be captured during the original clinical trial.

8. Trial Hypothesis

8.1 Primary effectiveness endpoint

The objective of the first primary effectiveness analysis is to demonstrate significant within-subject improvement of word recognition in quiet as evaluated with the Consonant-Nucleus-Consonant (CNC) test through 3 years postactivation.

The objective is represented by the following hypotheses:

$H_0: \Delta_F \leq 0,$

$H_a: \Delta_F > 0,$

where:

Δ_F is the mean change in CNC word recognition score from the baseline pre-operative CNC word recognition score.

Estimated within-subject means and mean changes from baseline will be reported with 95% CI for the overall comparison and at each follow-up time interval.

For the primary effectiveness objective, the analyses will be carried out using the 5 time intervals, treated as categorical measures in the models: 3 months post initial activation (IA), 6 months post IA, 12 months post IA, and annually up to 3 years post IA.

8.2 Secondary effectiveness endpoint

The objective of the second primary effectiveness endpoint is to demonstrate significant improvement of sentence recognition in noise (+5dB SNR and/or +10dB SNR) as evaluated with the AzBio test through 12 months postactivation. Note that subjects will be evaluated in the best unilateral condition with the AzBio sentences at a +5 signal-to-noise ratio. If the subject scores ≤ 20% correct then the remaining conditions will be tested using a +10 dB signal-to-noise ratio. If the subject scores > 20% correct then remaining conditions will continue to be tested using a +5 dB signal-to-noise ratio.

The objective is represented by the following hypotheses:

$H_0: \Delta_F \leq 0,$

$H_a: \Delta_F > 0,$

where:

Δ_F is the mean changes in AzBio sentence recognition score from the pre-operative AzBio sentence recognition score

Estimated within-subject means and mean changes from baseline will be reported with 95% CI for the overall comparison and at each follow-up time interval.

8.3 Additional effectiveness analyses

The primary analyses for each of the effectiveness endpoints will be based on the unilateral listening condition. As an additional exploratory analysis, the analysis for each effectiveness endpoint will also be analyzed under the other tested conditions (i.e. best bilateral – combined or bimodal).

9. Sample Size Considerations

Data collected in this study will include 50 newly implanted subjects. This data will be combined with data from other sources to support an analysis of safety and an analysis of effectiveness. The three sources of data include:

1) 50 subjects from this New Enrollment study.
2) 35 subjects in continued follow-up from the Hybrid Extended Duration post approval study.
3) A minimum of 65 subjects implanted outside of this New Enrollment post approval study following device approval and commercial availability using standard of care techniques.

Data on these three groups will be aggregated for the primary analysis of safety. Data from the first two groups (i.e. the New Enrollment study and Hybrid Extended Duration study) will be aggregated for the primary analysis of effectiveness.

Attrition is expected to be approximately 20% in the New Enrollment Study. For safety, the combined data sources are expected to yield 150 subjects through 3 years. For effectiveness, the combined data sources are expected to yield at least 75 through 3 years.

9.1 Sample Size Estimation for Primary Safety Endpoints

For characterizing the incidence of adverse events over time, such as the occurrence of low frequency hearing loss, a total of 150 subjects would provide a precision (defined as the half-width of a two-sided 95% confidence interval) of approximately 8.3% or smaller. This calculation is based on an exact binomial confidence interval. Sample size calculations were

conducted in PASS 14 (NCSS, LLC., Kaysville, UT) using the "Confidence Intervals for One Proportion" option.

9.2 Sample Size Estimation for Effectiveness Endpoints

Speech performance data on between 50 and 100 subjects will provide a precision of between 4.7% and 8.2% based on a standard deviation of approximately 29% as observed in the Hybrid L24 PMA data for the change in CNC and AzBio scores from preoperative to 3 years

Sample size calculations were conducted in PASS 14 (NCSS, LLC., Kaysville, UT) using the "Confidence Intervals for One Mean" option.

9.3 Final Sample Size

With the total sample size, the precision for study endpoints will be in an acceptable range. Sample size calculations based on simple means are conservative as the planned analysis based on the repeated measures model properly incorporates more information and should provide for improved precision.

9.4 Safety Analysis

All safety analyses will be performed on the ITT study population and include the data from the IDE study and the [redacted].

9.4.1 Primary Safety Endpoint

An Adverse Event is the development of an untoward medical occurrence or the deterioration of a pre-existing medical condition following or during exposure to an investigational product, whether or not considered causally related to the product or the surgical procedure to implant it. An untoward medical condition can be symptoms (e.g., nausea), signs (e.g., tachycardia, fever) or clinically significant abnormal results of an investigation (e.g., laboratory findings, chest x-ray).

Adverse events that occur during this study may be associated with the implant procedure, including those from general anesthesia, or specifically associated with the use of the device. An adverse event will be considered to be device-related when, in the judgment of the Primary Investigator, there is a logical connection between the use of the device and the occurrence of the event, above and beyond the study procedure itself. Adverse events associated with cochlear implantation in previous investigations include tinnitus, dizziness, swelling, facial nerve stimulation, and open and/or short circuit electrodes, among others.

Adverse events will be counted regardless of severity, seriousness, onset, duration, or relation to study treatment. Device specific adverse events include loss of hearing sensitivity at implant ear (defined as loss reaching a PTA average of 90 dB or greater for frequencies 125-1000Hz), total loss, and/or explantation.

A serious adverse event (SAE) is any untoward medical occurrence which:

- Results in death;
- Is life-threatening;
- Requires in-patient hospitalization for > 24 hours or prolongation of hospitalization which is not specifically required by the protocol;
- Results in permanent impairment of a body function or permanent damage to a body structure; or

- Requires medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

For any SAE, if the Primary Investigator judges that there is a logical connection (caused or contributed to) between the use of the device and the occurrence, the SAE will be notes as device-related.

All adverse event rates will be reported as the number and frequency of events with corresponding 95% exact binomial confidence limits, as well as the number of events per patient-time (e.g., events per 10 patient years). These values will be qualitatively compared to the same rates observed in the pivotal IDE study; no formal statistical comparisons will be conducted.

9.4.2 Secondary Safety Endpoint

Secondary safety endpoints will include the following:

- Cumulative Safety Assessment: Adverse events with start dates prior to initial activation and each follow-up time interval will be tabulated.
- Procedure-Related Adverse Event Assessment: Procedure-related events occurring during the follow-up period will be tabulated.
- Device-Related Adverse Event Assessment: Device-related events occurring during the follow-up period will be tabulated.
- The above two classes of events (procedure and device related) will be summarized as rates. The numerator for each rate will be the number of subjects with at least one procedure (or device) related adverse event. The denominator will be the total number of subjects.
- Rates (overall and procedure and device related) will also be summarized by type.
- Time to first adverse event (including total losses of residual hearing) will be summarized using Kaplan Meier plots. Exploratory proportional hazards regression models will be used to determine whether demographics and baseline characteristics are associated with risk for adverse events over follow-up. Hazard ratios and 95% confidence intervals for these analyses will be cited.

9.5 Poolability

Since this is a single-arm, multi-center study with data from different cohorts, analyses will be performed to assess potential heterogeneity of outcomes. This will be done separately for sites and for cohorts (i.e. the New Enrollment Study, Extended Duration Study, and RWE study). For the primary safety endpoint, a binary endpoint, a Cochrane-Mantel-Haenszel test for differences by group (i.e. sites, cohorts) will be performed at the 0.10 alpha level. For the primary and secondary effectiveness endpoints, a test of differences of means by group (i.e. sites, cohorts) will be performed at the 0.10 alpha level based on a repeated measures regression model (allowing for repeated measures on subjects over time).

9.6 Other Data

Protocol deviations will be listed and summarized.

10. Version History

Version	Date	Changes
DRAFT	06 July 2014	Initial draft.
1.0		Initial version.
2.0	05 September 2014	Primary Effectiveness Analysis – 8 intervals including baseline.
3.0	16 September 2014	Alignment with v5 of the protocol, including updates to testing of the secondary primary endpoint at +5 signal-to-noise ratio with qualified testing at +10.
4.0	17 July 2017	Alignment with v7 of the protocol, including incorporation updates to the sample size and subgroup analysis plans. Clarified the testing condition for the effectiveness endpoints.
5.0	29 April 2022	Reduced study follow-up to 3 years postactivation.