Statistical Analysis Plan

Post Approval Study – Longitudinal Monitoring of Subjects with the Nucleus Hybrid L24 Cochlear Implant

CAM-5573-HYB-PMA

April 17, 2014
Version 1.0

Study Sponsor:

Cochlear Americas
13059 East Peakview Avenue
Centennial, CO 80111

1.0 Table of Contents

2.0 Data Analyses

2.1 Study Population

In addition to this study of 100 newly- implanted Hybrid subjects there are at least an additional 38 eligible subjects drawn from the original cohort of 50 subjects in the Hybrid L24 pivotal IDE study to be followed longitudinally to a natural 5 year post-activation end point. To be more specific, of the 50 pivotal IDE subjects 10 subjects were explanted and/or discontinued participation, and an additional 5 have already met the 5 year post-activation interval. However, safety data and efficacy data will be available on a minimum 150 subjects in total as these subjects will be included in the total analysis. In addition 3 subjects have been implanted with the Nucleus Hybrid L24 cochlear implant as part of the Hybrid L24 – Continued Access IDE supplement and will also be included in the overall data set.

.

2.2 Sample Size

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. Additionally, speech performance can be well characterized with a cohort of 50 subjects as demonstrated by the original Hybrid L24 PMA data. Further, with this planned sample size for the combined cohorts, speech performance data on between 50 and 150 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 6 months.

We will make every attempt to maintain a follow up rate of 80% for the PAS and agree with 80% (or above) as our primary target. However, in reviewing our past study experiences, an 80% follow up rate may be unrealistic in the industry, especially given that the device will be approved for use and available without participation in the PAS.

The length of the study will likely also affect subject retention negatively. For example, in the pivotal trial we had 4% subject withdrawal at the 12 month interval. If this rate of withdrawal is consistent in the PAS we would expect at a minimum roughly 20% of subjects to withdraw from the study by the 5 year point. Given the length of the study and the availability of the technology, the attrition rate will likely be higher than what was

seen at a 12 month test interval in the pivotal trial. We will not coerce subjects to continue in the study if they choose to withdraw.

Additionally, a smaller sample size could still ensure the scientific integrity of the study. When the two cohorts are combined, there is a possibility of 138 subjects enrolled in either arm of the study (38 from the exiting arm, 100 from the newly implanted). As currently noted in the post approval study protocols, data on between 50 and 150 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 6 months). If we achieve a 70% follow up rate on the newly enrolled arm of the study we will have data for 70 subjects, without including the existing arm of the study (i.e., Extended Duration). As the sample size for the post approval studies are based on precision arguments and not formal statistical hypothesis tests, we believe this rate of 70% is still appropriate however will comply with the agencies request for an 80% follow up rate.

3.0 Safety

3.1 Primary Safety Objective

The primary safety outcome of this study is related to the long term safety (five years) of the Hybrid L24 implant. Safety of the Hybrid L24 implant will be monitored based on type and frequency of adverse events. 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 (including the surgical procedure) and the occurrence of the event. Those adverse events (by type and frequency of occurrence) will be expected to be consistent with that reported in the pivotal study.

The degree of preservation of low-frequency hearing will be assessed as part of the safety data at each study interval.

3.2 Analysis of Primary Safety Objective

Adverse Events and Serious Adverse Events will be expressed as events per patient – time.

All adverse event rates will be reported as the number and frequency of events with corresponding 95% exact binomial confidence limits and the number of events per patient-time (e.g., events per 10 patient years), and compared to the adverse events from G07019 (Hybrid L24 pivotal study).

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

4.0 Efficacy

4.1 Primary Efficacy Objective

The long-term effectiveness of the device will be assessed based on individual performance as measured by speech perception tests over the course of the 5 year study duration. These tests (CNC words in quiet and AzBio sentences at both +5 dB and +10 dB SNR) will be administered aided at the preoperative interval. Post-activation intervals and outcomes will be based on a comparison between the hearing aid (preoperative) and 5 year post-activation speech perception data.

The co-primary efficacy endpoints for this study will be the assessment of statistical significance of the within-subject differences for two speech recognition tests:

- Word recognition in quiet as evaluated with the Consonant-Nucleus-Consonant (CNC) test (Peterson and Lehiste, 1962);
- Sentence recognition in noise (+5dB and +10 dB)) as evaluated with the AzBio test (Spahr et al., 2011).

Scores on both speech tests will be obtained pre-implant with hearing aids, at the 3-month, 6-month and 12 month post-activation interval and at annual follow-ups thereafter until study completion at 5 years post-activation.

In an attempt to standardize speech assessment methods across commercial implanting centers, the above metrics were chosen based on the Minimum Speech Test Battery (MSTB) published in 2011 as a joint effort of the cochlear implant industry and the audiologic/ otologic professional community. These test materials are provided free of charge to any cochlear implanting center and include calibration and instructions for use.

4.2 Analysis of Primary Efficacy Objective

The significance of the mean differences in speech recognition scores between preoperative and the post-implant interval will be analyzed using maximum likelihood based repeated measures linear regression models. If there is significant evidence that

the assumption of normality does not hold (i.e., $p < 0.05$ from a Shapiro-Wilk test of normality), then ranked data will be used in the repeated measures models.

5.0 Additional Statistical Analyses

5.1 Analysis Cohorts

The primary analysis will be based on all available subjects. Additional analyses will examine the following cohorts to better understand the long term device performance and the effects of loss of residual hearing and/or device explant.

5.1.1 *Subjects with low frequency hearing loss*

The subset of subjects experiencing loss of residual hearing during the course of the study will be modeled with repeated measures linear regression models. This analysis will characterize both the speech performance of these subjects up through the loss of low frequency hearing with the original implant and also for speech performance measured post-intervention (i.e. traditional cochlear implant) for those subjects who experience receive an intervention to address their low frequency hearing loss. This will characterize their performance up through their loss of low frequency hearing point and characterize the performance of these subjects following intervention to address low frequency hearing loss.

5.1.2 *Explant/revision subjects*

The subset of subjects experiencing either an explant or device revision, for any reason, will be modeled with repeated measures linear regression models, first only utilizing the speech performance data up to the point of explant or revision. This will characterize their performance up to this point and time. Second, the same model will be applied to data collected on these subjects post explant/revision. This will characterize the performance of these subjects following an explant or revision to help better understand the consequences of the treatment strategy.

5.2 Analysis of Baseline Covariates

The effect of baseline covariates on the co-primary efficacy measures will be assessed. This will be based on univariable and multivariable regression models. Baseline covariates to be explored include age at implantation, gender, duration of hearing loss, duration of severe hearing loss, pre-operative speech perception score, and pre-operative low-frequency hearing threshold.

6.0 Justification of Pooling Across Study Sites

Pooling data from study sites will be done based on the following: all sites will have the same protocol, the sponsor will monitor the sites to assure protocol compliance, and the data gathering mechanism (case report forms and data acquisition) will be the same across all study sites (Meinert, 1986).

7.0 Missing Data

All efforts will be put forth to ensure near complete follow-up, with particular focus on the assessment of the primary outcome and occurrence of adverse events. Regular reminders of subject follow up due dates will be provided to participating centers to facilitate scheduling of follow-up visits. The target retention rate for this study is at least 80%. In the event that a follow up due date is missed, the Sponsor will instruct the participating center to make three attempts to contact the study subject and inform them of the need to be tested. The third and final attempt will be in writing and if no response is received then the subject will be considered to have withdrawn from the study.

8.0 References

Meinert, C. (1986). Clinical Trials: Design, Conduct, and Analysis. Oxford University Press, New York.