STATISTICAL ANALYSIS PLAN

for

Safety and Efficacy of the Cochlear™ Nucleus® CI422 Cochlear Implant in Adults (IDE# G120234)

April 2014

Version 2.0

Study Sponsor:

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1.0 Data Analyses

1.1 Study Population

Any subject in whom the Cochlear Nucleus CI422 cochlear implant is attempted to be implanted under this protocol will comprise the intention-to-treat population (ITT). The primary efficacy and safety endpoints will be evaluated with the ITT population. A tipping point sensitivity analysis will be conducted by the methods described in the missing data section to address any missing data.

The effectiveness analyses will also be done on the completed cases (CC) population; treated subjects who had follow-up of the primary endpoint at the protocol prescribed time. A supportive analysis of the primary endpoint will be done in the CC population. Additional analyses will be examined only in the CC population.

1.2 Sample Size

A total sample size of 50 evaluable subjects is planned. An allowance of 10% to account for possible attrition is planned such that up to 55 subjects may be recruited into the study and implanted. The planned sample size of 50 subjects will provide adequate power for the primary efficacy endpoint based on a range of assumptions. Power for this test under a variety of assumptions is provided below. Calculations are based on a one-sample t-test at a two-sided 0.05 alpha level.

Table 1. Power for Sample Size of 50 Evaluable Subjects

True Population CNC Word Score Mean Change	True Population CNC Word Score Standard Deviation for Change		
	30%	**40%**	**50%**
20%	>99%	93%	79%
25%	>99%	99%	93%

1.3 Safety

1.3.1 Primary Safety Objective

The purpose of this objective is to describe the safety of cochlear implantation with the CI422 implant in newly implanted adults with expanded indications for candidacy. Safety for this objective will be defined as follows: medical/surgical and device related adverse events will be no worse than with the current approved labeling with regard to type, frequency and seriousness. To address this endpoint, the number and percent of

patients with a device or procedure related adverse event through 6 months postactivation will be reported and tabulated for comparison to current approved labeling (CI422 Physicians Package Insert). Adverse events will be summarized by event type, frequency, seriousness, and whether they are medical/surgical and/or device related. Additionally, any subject at 6 months who experiences a >15 dB shift from their preoperative low frequency (125-1,000 Hz) pure tone average resulting in a low frequency pure tone average of greater than 90dB HL will be reported as an adverse event under this protocol.

1.3.1.1 Analysis of Primary Safety Objective

The number of events, and number and percentage of subjects with each event will be tabulated for adverse events overall and by type. Events will be characterized by severity, seriousness and relatedness. Binomial exact, two-sided, 95% confidence limits will be calculated for device and procedure related adverse event rates.

1.3.2 Secondary Safety Objective

The purpose of the ~~secondary~~ safety objective is to describe resulting hearing levels for each subject at the 6 month endpoint of the study. It is anticipated that no more than 50% of study subjects will present at 6 months with a >15 dB shift from their preoperative low frequency (125-1,000 Hz) pure tone average, resulting in a low frequency pure tone average of greater than 90dB HL. For those subjects who experience the described shift in hearing, it is anticipated that most (>75%) of those subjects will experience an increase in CNC score at 6 months of at least 20% over their preoperative CNC score in the best unilateral condition (treated ear). The CNC Word score in best unilateral condition preoperatively and at 6 months will be compared on a paired per-patient basis, and the number and percentage of subjects for whom the 6 month score is at least 20% better than the preoperative score will be reported. There is no planned formal statistical hypothesis test for this endpoint.

1.4 Efficacy

Efficacy of the Cochlear Nucleus CI422 cochlear implant system will be determined by a comparison of preoperative vs. postoperative outcomes measures. The speech measures for this purpose are the CNC Word Test and the AzBio sentences in noise. The primary and secondary efficacy endpoints will be based on analyses of designated test measures at the 6-month postactivation interval.

1.4.1 Primary Efficacy Objective

The Primary Efficacy Objective for this study is to understand if cochlear implantation with a Cochlear Nucleus CI422 cochlear implant in adult patients with expanded indications results in improved speech understanding at 6 months postactivation, as measured by performance on an open-set word recognition test, in the best unilateral listening condition of the implanted ear.

- On the CNC word measure, the group mean score for best unilateral listening condition at 6 months will be better than the group mean score in the preoperative, unilateral aided condition.

The primary hypothesis to be tested in this analysis is the following: that the 6 month postoperative performance is significantly different from preoperative performance in the treated ear. The null and alternative hypotheses are given below.

$H_{01}: ì_{Post} - ì_{Pre} \leq 0$ versus $H_{a1}: ì_{Post} - ì_{Pre} > 0$

Where $ì_{Pre}$ is the CNC word score in quiet obtained with a hearing aid preoperatively in the ear to be implanted, and $ì_{Post}$ is the CNC word score in quiet obtained at 6 months post sound processor activation in the treated ear. The test will be based on a one-sample t-test of the paired difference in pre and post results and performed at the one-sided 0.025 alpha level.

1.4.2 Secondary Efficacy Objectives

Secondary efficacy objectives will be determined by further comparison of group means for preoperative vs. 6 months postoperative outcome measures in best unilateral and best bilateral listening conditions. The speech measures for this purpose are the CNC Word Test and the AzBio sentences in noise.

Secondary efficacy endpoints are as follows:

- On the CNC word measure, the group mean score for best bilateral listening condition at 6 months will be better than the group mean score in the preoperative, bilateral aided condition.
- On the AzBio sentences-in-noise measure, the group mean score for best bilateral listening condition at 6 months will be better than the group mean score in the preoperative, bilateral aided condition.
- On the AzBio sentences-in-noise measure, the group mean score for best unilateral listening condition at 6 months will be better than the group mean score in the preoperative, unilateral aided condition.

The hypothesis test for each of the secondary efficacy endpoints is as follows:

$H_{01}: ì_{Post} - ì_{Pre} \leq 0$ versus $H_{a1}: ì_{Post} - ì_{Pre} > 0$

Where $ì_{Post}$ is the post-implant value and $ì_{Pre}$ is the pre-implant value. Each test will be based on a one sample paired t-test of the difference in pre and post results. All tests will be performed at the one-sided 0.025 alpha level.

1.4.3 Type I Error Control

The secondary efficacy objectives will be tested only if the primary efficacy objective is successful. Each secondary objective will be tested sequentially with the subsequent test performed only if the first is successful. Therefore, the overall Type I error of 5% is

preserved and no increase in sample size to protect against multiplicity is required. The sequential order of the testing procedure is as follows:

1. Bilateral 6 month CNC Word measure
2. Bilateral 6 month AzBio sentences-in-noise measure
3. Unilateral 6 month AzBio sentences-in-noise measure

1.5 Additional Statistical Analyses

1.5.1 Analysis of Baseline Characteristics

The baseline characteristics of the study groups will be presented descriptively. Quantitative variables such as age will be presented with mean, standard deviation, median, minimum and maximum. Qualitative variables such as gender will be presented with number with the condition, the sample size, the percentage, and the 95% two-sided exact binomial confidence intervals.

1.5.2 Supportive Efficacy Analyses

Supportive efficacy analyses will include analysis of individual data for all measures. Individual scores obtained at 6 months will be compared with those obtained, on the same measures preoperatively, based on the binomial model where appropriate (see Thornton and Raffin, 1978) to establish the proportions of those subjects showing improvement, no change, and decrement in performance including:

- On the CNC word measure, most (> 75%) of the subjects at 6 months will score equal to or better in their best unilateral listening condition than they did in the preoperative unilateral aided condition.
- On the AzBio sentences-in-noise measure, most (> 75%) of the subjects at 6 months will score equal to or better in their best unilateral listening condition than they did in the preoperative, unilateral aided condition.
- On the CNC word measure, most (> 75%) of the subjects at 6 months will score equal to or better in their best bilateral listening condition than they did in the preoperative, bilateral aided condition.
- On the AzBio sentences-in-noise measure, most (> 75%) of the subjects at 6 months will score equal to or better in their best bilateral listening condition than they did in the preoperative, bilateral aided condition.

Regression analyses of efficacy parameters will also be done, adjusted for baseline covariates of interest including:

- Age at implantation
- Duration of hearing loss
- Gender

Longitudinal analyses (to 12 months) of efficacy parameters will be analyzed. In addition, change in low-frequency hearing sensitivity (125 to 1000 Hz) for each subject will be documented and ultimately reported as the total number and percentage of subjects who fall within the ranges given in the following table. The impact of any such changes will be assessed in light of overall speech perception outcomes.

Change in low-frequency hearing sensitivity
≤10 dB
>10 dB and ≤20 dB
>20 dB and ≤30 dB
>30 dB

1.6 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). Maximum enrollment at individual sites will be set at 10 subjects, in an attempt to improve generalizability of the results.

Consistency of the primary efficacy endpoints between sites will be assessed by testing for a difference between sites in the change in CNC word score from preoperative to 6 months postoperative via an analysis of variance model, with the change in CNC word score as the outcome and site as the factor. A p-value for the site factor of less than 0.10 will be considered evidence of differences between sites for the primary efficacy outcome. If there is evidence of a difference, additional analyses will be performed to explore the possible role of baseline characteristics to explain the results. Results for the primary efficacy endpoint will also be presented separately by site, irrespective of the test of differences between sites to help understand both qualitative and non-significant differences between sites.

1.7 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.

In the event a subject is withdrawn prior to the 6-month assessment, the primary analysis of the primary efficacy endpoint will involve imputing the pre-operative CNC word test score for the 6 month CNC word test. This is equivalent to treating each subject with a missing 6 month result as unchanged from baseline. The p-value for the primary efficacy statistical hypothesis test will be calculated using this imputation to understand the impact of missing data on the primary result.

2.0 References

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