Official Title: A pivotal, prospective, multi-center, open-label study evaluating the safety and effectiveness of the Cochlear™ Osia® 2 System in a pediatric population

NCT Number: NCT05000931

Document Date: 09 August 2021

[redacted]

Cochlear Americas

A pivotal, prospective, multi-center, open-label study evaluating the safety and effectiveness of the Cochlear™ Osia®2 System in a pediatric population.

CAM5766, CIP Version 3.0

Statistical Analysis Plan

Version 1.0, 09Aug2021

Version History

Version	Version Date	Author/Title	Summary of Key Changes
0.1	07Dec2020	[redacted]	Initial Release
0.2	19Jan2021	[redacted]	Revised due to 16Dec2020 FDA Study Design Considerations
1.0	09Aug2021	[redacted]	Updated version numbering to align with eTMF system. Updated time point for PTA secondary endpoint.

[redacted]

Cochlear

NAMSA

Sponsor	Study	Version
Cochlear Americas	**A pivotal, prospective, multi-center, open-label study evaluating the safety and effectiveness of the Cochlear™ Osia® 2 System in a pediatric population**	**1.0**

Document Approval

Author	
Authored By	[redacted]
Signature	
Date	
Role	

Approval	
Approved By	[redacted]
Signature	
Date	
Role	

Approval		
Approved By	[redacted]	
Signature		
Date		
Role		

Table of Contents

1 Introduction

This statistical analysis plan (SAP) describes the planned statistical methods to be used during the reporting and analysis of data collected under the Clinical Investigation Protocol CAM5766, A pivotal, prospective, multi-center, open-label study evaluating the safety and effectiveness of the Osia 2 System in a pediatric population. This SAP should be read in conjunction with the study clinical investigation plan (CIP) and case report forms (CRFs). This version of the SAP has been developed with respect to the Clinical Investigation Protocol Version 3.0, 05AUG2021. Any revisions to the protocol or CRFs that impact the planned analyses may require updates to the SAP.

2 Study Objectives

The clinical investigation is a pivotal, prospective, multi-center, open-label clinical investigation evaluating the safety and effectiveness of the Osia 2 System in a pediatric population. The primary intent for this study is to support regulatory approval for the Osia 2 System in this population.

Specific objectives of the study are as follows:

Primary

- To demonstrate the safety of the Osia 2 System in a pediatric population aged 5 – 11 years by quantifying the type, frequency and severity of adverse events

Secondary

- To compare preoperative performance compared to postoperative performance in parental questionnaires using the Osia 2 System.
- To compare preoperative unaided bone conduction thresholds to postoperative unaided bone conduction thresholds.
- To compare unaided preoperative speech perception performance to aided speech perception performance postoperatively using the Osia 2 System.
- To compare unaided preoperative adaptive speech in noise performance to aided adaptive speech in noise performance using the Osia 2 System.

2.1 Study Endpoints

There is one primary and four secondary endpoints defined for this study.

3 Study Design

This is a prospective, multi-center, open-label clinical investigation. Expected enrollment is 12 months with an expected duration per subject of 12-18 months.

4 Sample Size Determination

Sample size for the study is not driven by power requirements for a formal statistical hypothesis test. The planned sample size of 50 subjects will provide data to characterize safety and effectiveness with a reasonable degree of statistical precision. Additionally, the planned sample size will allow for a high probability of observing events of interest. For example, with 50 subjects, the half-width of a two-sided 95% confidence interval for a continuous endpoint based on a t-distribution would be 0.284 units on the effect size scale. Similarly, with 50 subjects, there is a greater than 95% probability of observing one or more events that occur at a population rate of 5.9%

5 Statistical Analyses

5.1 General Considerations

Except where otherwise specified, the following general principles apply to the planned statistical analyses. All statistical analysis will be conducted using SAS version 9.4 or later (SAS Institute Inc., Cary, NC) or other widely-accepted statistical or graphical software as required.

5.1.1 Descriptive Statistics

Continuous data will be summarized with mean, standard deviation, median, minimum, maximum, and number of evaluable observations. Categorical variables will be summarized with frequency counts and percentages. Confidence intervals may be presented, where appropriate, using the t-distribution for continuous data and Clopper-Pearson Exact method for categorical variables.

5.1.2 Visit Windows

Unless otherwise specified, visit based assessments will be analyzed for each analysis time point according to the nominal visit entered in the Case Report Form (CRF) regardless of if it is out of window. Windows are defined in the CIP as follows: Visit 1 2 week follow up = +/- 7 days, Visit 2 Device Fitting = +/- 7 days; Visit 3 3 Months +/- 14 days, Visit 4 6 months +/- 14 days, and Visit 5 12 Months +/- 14 days.

5.1.3 Statistical Significance

Unless otherwise specified, hypothesis testing will be performed at the two-sided 0.05 significance level. P-values will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as "<0.001". If a p-value is greater than 0.999, it will be reported as ">0.999".

5.2 Analysis Populations

Analysis will be based on subjects who are successfully implanted with the device.

5.3 Handling of Missing Data

All attempts will be made to limit the amount of missing data. Imputation for specific endpoints are outlined in the description of each endpoint. Unless otherwise specified, no attempt will be made to impute missing data. If a data point is missing, that data point will not contribute to that portion of the analysis. The number of evaluable observations will be reported in analysis so that extent of missing data can be assessed.

5.4 Subject Disposition

The number of subjects in each analysis population will be presented along with reason for any exclusions. Subject accountability will be summarized by visit. The number of subjects who are enrolled, eligible for follow-up, and number completing clinical follow-up will be summarized for each protocol-required visit. In addition, the number of subjects who complete the study or exit early will be summarized by reason.

5.5 Demographics and Baseline Characteristics

Descriptive statistics will be presented for all clinically relevant baseline demographic, medical history, and clinical characteristic variables.

5.6 Analysis of Study Endpoints

There is one primary endpoint and four secondary endpoints. Formal statistical hypothesis tests are planned for the secondary endpoints.

The overall type I error rate will be maintained via a gatekeeping approach whereby statistical tests will proceed in order until a non-significant test is obtained, at which point, formal testing for the purposes of labeling claims will cease.

5.6.1 Primary Endpoint

The primary endpoint is device and procedure related adverse events Surgery through Visit 4 (6 Months). Events will be summarized by type, frequency, and severity.

5.6.1.1 Primary Analysis of the Primary Endpoint

There is no formal hypothesis test for the primary endpoint.

The endpoint will be presented in tabular format, displaying the number and percentage of subjects with adverse events. Events will also be summarized by type and severity. Results will be based on observed events without imputation.

5.6.2 Secondary Endpoint 1 - SSQ

The secondary endpoint 1 is defined as the difference between preoperative and postoperative performance on the Speech Spatial & Qualities of Hearing Questionnaire (SSQ) – Parent version at 6 months post-surgery.

5.6.2.1 Primary Analysis of Secondary Endpoint 1

Secondary endpoint 1 will be assessed with the following hypothesis:

$H_0: \Delta \leq 0$

$H_a: \Delta > 0$

where Δ represents difference between preoperative and postoperative performance on the Speech Spatial & Qualities of Hearing Questionnaire (SSQ) – Parent version at 6 months post-surgery, specifically $\Delta = SSQ_{6\ Months} - SSQ_{preop}$. This difference is parameterized so that a positive value is indicative of a clinical improvement in the questionnaire.

The hypothesis will be evaluated using a one-sample, one-sided 0.025 alpha level t-test for a mean against the null of zero. The objective will be met if the null hypothesis is successfully rejected.

The endpoint will be presented with descriptive statistics and the corresponding two-sided 95% confidence interval based on the t-distribution.

5.6.2.2 Handling of Missing Data

Little missing data is expected for this endpoint. If there is missing endpoint data, a multiple imputation approach will be used based on a fully conditional specification. The imputation model will include the following covariates: age, sex, and baseline SSQ. An augmented likelihood approach will be used if need

to facilitate modeling. A total of 100 imputed data sets will be generated and results combined for inferential purposes.

5.6.2.3 Sensitivity Analysis

In the event there is significant evidence of a departure from normality based on a Shapiro-Wilk test at the 0.05 alpha level, a one-sample Sign test (a non-parametric alternative) will be employed.

A tipping point analysis for missing data will be performed as a sensitivity analysis. This will impute values for the missing endpoint data, using all possible combinations of the "best" and "worst" observed results for the endpoint (i.e. all missing imputed as "worst", all missing imputed as "best", and all combinations between these extremes).

5.6.3 Secondary Endpoint 2 – PTA

Secondary endpoint 2 is defined as the mean difference in individual subject PTA 500, 1, 2, and 4kHz Baseline to 4 Weeks post-surgery.

5.6.3.1 Primary Analysis of Secondary Endpoint 2

The secondary endpoint 2 will be assessed with the following hypothesis:

$H_0: \Delta \leq 0$

$H_a: \Delta > 0$

where Δ represents difference between baseline PTA and 4 Weeks-post surgery PTA, specifically $\Delta = PTA_{4\ Weeks} - PTA_{preop}$. This difference is parameterized so that a positive value is indicative of a clinical improvement.

The hypothesis will be evaluated using a one-sample, one-sided 0.025 alpha level t-test for a mean against the null of zero. The objective will be met if the null hypothesis is successfully rejected.

The endpoint will be presented with descriptive statistics and the corresponding two-sided 95% confidence interval based on the t-distribution.

5.6.3.2 Handling of Missing Data

Little missing data is expected for this endpoint. If there is missing endpoint data, a multiple imputation approach will be used based on a fully conditional specification. The imputation model will include the following covariates: age, sex, and baseline PTA. An augmented likelihood approach will be used if need to facilitate modeling. A total of 100 imputed data sets will be generated and results combined for inferential purposes.

5.6.3.3 Sensitivity Analysis

In the event there is significant evidence of a departure from normality based on a Shapiro-Wilk test at the 0.05 alpha level, a Sign test (a non-parametric alternative) will be employed.

A tipping point analysis for missing data will be performed as a sensitivity analysis. This will impute values for the missing endpoint data, using all possible combinations of the "best" and "worst" observed results for the endpoint (i.e. all missing imputed as "worst", all missing imputed as "best", and all combinations between these extremes).

5.6.4 Secondary Endpoint 3 – CNC Words

Secondary endpoint 3 is defined as the mean difference between baseline unaided speech perception in quiet and the aided condition using the Osia 2 system at 6 months post-surgery on open-set monosyllabic word recognition (CNC Words) in quiet.

5.6.4.1 Primary Analysis of Secondary Endpoint 3

The secondary endpoint 3 will be assessed with the following hypothesis:

$H_0: \Delta \leq 0$

$H_a: \Delta > 0$

where Δ represents difference between baseline unaided speech perception CNC and 6 months-post surgery CNC, specifically $\Delta = CNC_{6\ Months} - CNC_{preop}$. This difference is parameterized so that a positive value is indicative of a clinical improvement.

The hypothesis will be evaluated using a one-sample, one-sided 0.025 alpha level t-test for a mean against the null of zero. The objective will be met if the null hypothesis is successfully rejected.

The endpoint will be presented with descriptive statistics and the corresponding two-sided 95% confidence interval based on the t-distribution.

5.6.4.2 Handling of Missing Data

Little missing data is expected for this endpoint. If there is missing endpoint data, a multiple imputation approach will be used based on a fully conditional specification. The imputation model will include the following covariates: age, sex, and baseline CNC. An augmented likelihood approach will be used if need to facilitate modeling. A total of 100 imputed data sets will be generated and results combined for inferential purposes.

5.6.4.3 Sensitivity Analysis

In the event there is significant evidence of a departure from normality based on a Shapiro-Wilk test at the 0.05 alpha level, a Sign test (a non-parametric alternative) will be employed.

A tipping point analysis for missing data will be performed as a sensitivity analysis. This will impute values for the missing endpoint data, using all possible combinations of the "best" and "worst" observed results for the endpoint (i.e. all missing imputed as "worst", all missing imputed as "best", and all combinations between these extremes).

5.6.5 Secondary Endpoint 4 – BKB SIN

Secondary endpoint 4 is defined as the mean difference between baseline unaided speech perception in quiet and the aided condition using the Osia 2 system at 6 months post-surgery on an adaptive speech in noise test BKB SIN.

5.6.5.1 Primary Analysis of Secondary Endpoint 4

The secondary endpoint 4 will be assessed with the following hypothesis:

$H_0: \Delta \leq 0$

$H_a: \Delta > 0$

where Δ represents difference between baseline unaided speech perception BKB SIN test and 6 months-post surgery BKB SIN test, specifically $\Delta = BKB_{6\ Months} - BKB_{preop}$. This difference is parameterized so that a positive value is indicative of a clinical improvement.

The hypothesis will be evaluated using a one-sample, one-sided 0.025 alpha level t-test for a mean against the null of zero. The objective will be met if the null hypothesis is successfully rejected.

The endpoint will be presented with descriptive statistics and the corresponding two-sided 95% confidence interval based on the t-distribution.

5.6.5.2 Handling of Missing Data

Little missing data is expected for this endpoint. If there is missing endpoint data, a multiple imputation approach will be used based on a fully conditional specification. The imputation model will include the following covariates: age, sex, and baseline BKB SIN. An augmented likelihood approach will be used if need to facilitate modeling. A total of 100 imputed data sets will be generated and results combined for inferential purposes.

5.6.5.3 Sensitivity Analysis

In the event there is significant evidence of a departure from normality based on a Shapiro-Wilk test at the 0.05 alpha level, a Sign test (a non-parametric alternative) will be employed.

A tipping point analysis for missing data will be performed as a sensitivity analysis. This will impute values for the missing endpoint data, using all possible combinations of the "best" and "worst" observed results for the endpoint (i.e. all missing imputed as "worst", all missing imputed as "best", and all combinations between these extremes).

5.7 Poolability Analyses

All investigational sites will follow the requirements of a common protocol and standardized data collection procedures and forms. The primary and secondary endpoints will be presented separately for each site using descriptive statistics. Poolability of the primary endpoints across investigational sites will be evaluated using a regression model with fixed effects for site. For the primary endpoint, analysis will be based on the proportion of subjects experiencing a procedure or device related adverse event and a logistic regression approach. For the secondary endpoint, a linear regression approach will be used. If the p-value for the site effect is 0.15, additional exploratory analyses will be performed to understand any variations in outcomes by site.

5.8 Safety Analyses

Adverse events (AEs) will be tabulated with the number of events and subjects with event for each event type and overall. Rates will be reported as the number of subjects who experience at least one event during the analysis interval out of the total number of subjects with follow-up to the beginning of the analysis interval. Serious adverse events (SAEs) will also be tabulated.

All AEs and SAEs will also be summarized by relatedness as described above. Adverse events leading to death or study discontinuation will be provided in listing format.

5.9 Subgroup Analyses

Subgroup analysis of the primary and secondary endpoints will be performed for the following subgroups: sex, race (white vs. non-white), age at implantation and etiology of hearing loss. These analyses are intended to demonstrate consistency of results across subgroups.

For the primary safety endpoint, analysis will be based on the proportion of subjects experiencing a procedure or device related adverse event and a logistic regression approach.

5.10 Interim Analyses

No formal interim analyses for the purposes of early stopping for effectiveness or for adaptive sample size re-estimation are planned. Periodic reports on study progress may be reported to regulatory agencies. Regulatory submission is planned to follow the conclusion of the 6 month study visit. Data through 12 months will be considered supplemental.

5.11 Protocol Deviations

Deviations from the procedures outlined in the CIP will be reported by investigational sites on the CRF. Protocol deviations will be summarized for all deviations and by type with event counts and number of subjects with at least one deviation.

6 Changes from Planned Analyses

Any changes to planned statistical analyses determined necessary prior to performing the analyses will be documented in an amended Statistical Analysis Plan and approved prior to the analysis when possible. Any other deviations or changes from the planned analyses deemed necessary due to violation of critical underlying statistical assumptions, data characteristics, or missing data will be clearly described in the clinical study report with justification and rationale.

7 Subject Listings

Subject listings will be provided for the primary and secondary endpoints.