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Cochlear Americas

A post-market interventional cohort study evaluating the clinical efficacy of the Osia 2 system in the US Market

CAM5778, Version 3.0

Statistical Analysis Plan

Version 1.1, 24 Jun 2020

Sponsor	Study	Version
Cochlear Americas	**A post-market interventional cohort study evaluating the clinical efficacy of the Osia 2 system in the US Market**	**3.0**

Version History

Version	Version Date	Author/Title	Summary of Key Changes
1.0	19JUN2020	[redacted]	Initial Release
1.1	24JUN2020	[redacted]	Revised subject population & secondary endpoint

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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; A post-market interventional cohort study evaluating the clinical efficacy of the Osia 2 system in the US Market. 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 A post-market interventional cohort study evaluating the clinical efficacy of the Osia 2 system in the US Market, Version 3.0 June 19, 2020. Any revisions to the protocol or CRFs that impact the planned analyses may require updates to the SAP.

2 Abbreviations

Abbreviation/Term	*Definition*
ADE	Adverse Device Effect
AE	Adverse Event
CIP	Clinical Investigation Plan
CRF	Case Report Form
DD	Device Deficiency
eCRF	Electronic Case Report Form
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect

3 Study Objectives

3.1 Primary Objective

The primary study objective is to evaluate the performance of the Osia 2 system on an adaptive speech in noise test.

3.2 Secondary Objective

To evaluate the safety of the Osia 2 system in a group of adult newly implanted recipients.

3.3 Study Endpoints

There is one primary endpoint and one secondary endpoint.

The primary endpoint is to demonstrate a significant difference between the aided and unaided conditions in Cohort 1 at 3 months using an adaptive speech in noise test when compared to the preoperative (Visit 1) unaided condition.

The secondary endpoint is to evaluate the safety of the Osia 2 system in a group of adult newly implanted recipients by estimating the incidence of device or procedure related adverse events.

4 Study Design

The study is a prospective interventional cohort study which consists of subjects implanted with the Osia 2 system.

4.1 Randomization

Test order for the 3-month interval will be randomly assigned in a 1:1 allocation ratio, stratified by site. Test order will be either aided followed by unaided, or unaided followed by aided.

4.2 Blinding

Blinding is not planned for this study due to feasibility concerns; specifically, the inability to conceal the presence or absence of the device from recipients or clinical investigators.

4.3 Study Assessments

The statistical analyses for the primary objective will be based on the 3-month assessment compared to the pre-operative baseline assessment. Analyses for the secondary objective will be based on safety data collected at the time of treatment and for the duration of the study up to and including 6 months.

5 Sample Size Determination

The planned sample size of 20 will provide greater than 80% power under a conservatively assumed mean of 12 and standard deviation of 15. Calculations are based on a one-sided 0.025 alpha and include allowance for attrition of up to 20%.

The primary objective is to evaluate the performance of the Osia 2 system on an adaptive speech in noise test. A paired t-test of superiority for the adaptive speech in noise test, comparing the aided and unaided conditions at 3-months relative to the preoperative (Visit 1) unaided condition. The mathematical statement of this hypothesis test is written as:

H0: $\Delta On \geq \Delta Off$

H1: $\Delta On < \Delta Off$

where ΔOn is the mean change in the adaptive speech in noise test between the 3-month aided (On) condition and the preoperative (Visit 1) unaided condition, and ΔOff is the mean change in the adaptive speech in noise test between the 3-month unaided condition (Off) and the preoperative (Visit 1) unaided condition. Successful rejection of the null hypothesis indicates the aided performance of the Osia 2 system is superior to the unaided performance based on the adaptive speech in noise test.

The secondary objective is to evaluate the safety of the Osia 2 system in a group of adult newly implanted recipients. Descriptive statistics specifically counts and percentages of device or procedure related adverse events captured through 6 months post-surgery will be summarized.

6 Statistical Analyses

6.1 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.

6.1.1 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.

6.1.2 Visit Windows

Visit windows and the schedule of study assessments are found in the CIP Section 3.

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 if it is out of window.

6.1.3 Statistical Significance

Hypothesis testing will be performed at the one-sided 0.025 significance level.

6.2 Analysis Populations

The following analysis populations are defined for analysis:

1. The ITT analysis cohort is defined as all implanted.

Analysis will be based on the intent-to-treat population. In order to obtain a complete ITT population, multiple imputation will be used for any missing outcome data.

6.3 Handling of Missing Data

Missing primary endpoint data will be imputed via multiple imputation analyses.

All attempts will be made to limit the amount of missing data. 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.

In the case of partial adverse event onset date or date of death, the unknown portion of the date of the event will be imputed. If the month and year are known, the 15th of the month will be used for analysis. If only the year is known, the event will be analyzed as if it occurred on June 30th of the known year. In the rare case that the date is fully unknown, the date will be imputed as the procedure date. Imputation of partial dates is subject to the condition that it must occur on or after the procedure date. In the case where the imputed date is prior to the procedure date, the date of the procedure will be used. As death cannot occur before any documented subject contact, for date of death the imputed date of death must occur on or after last known contact in study.

6.4 Subject Disposition

The number of subjects 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.

6.5 Demographics and Baseline Characteristics

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

6.6 Analysis of Study Endpoints

6.6.1 Primary Endpoint

The primary objective is to evaluate the performance of the Osia 2 system on an adaptive speech in noise test in Cohort 1.

6.6.1.1 Primary Analysis

A paired t-test of superiority for the adaptive speech in noise test, comparing the aided and unaided conditions at 3-months relative to the preoperative (Visit 1) unaided condition. The mathematical statement of this hypothesis test is written as:

H0: $\Delta On \geq \Delta Off$

H1: $\Delta On < \Delta Off$

where ΔOn is the mean change in the adaptive speech in noise test between the 3-month aided (On) condition and the preoperative (Visit 1) unaided condition, and ΔOff is the mean change in the adaptive speech in noise test between the 3-month unaided condition (Off) and the preoperative (Visit 1) unaided condition. Successful rejection of the null hypothesis indicates the aided performance of the Osia 2 system is superior to the unaided performance based on the adaptive speech in noise test.

The endpoint will be assessed in the ITT analysis cohort with complete data preoperatively and at 3 months.

6.6.1.2 Handling of Missing Data

In the event there are missing primary endpoint data the primary endpoint will be analyzed using a multiple imputation analysis. SAS PROC MI will be used to produce 100 imputed datasets. The imputed variable will be the difference between aided and unaided conditions at 3 months in the change in adaptive speech in noise test from preoperative. The following variables will be used as predictors in the model:

- Age
- Sex
- Pre-operative unaided adaptive speech in noise test

The estimates for the mean difference between aided and unaided change from pre-implant will be combined using PROC MIANALYZE providing an overall estimate for the primary endpoint, 95% confidence interval and one-sided p-value.

6.6.2 Secondary Endpoint

The secondary objective is to evaluate the safety of the Osia 2 system in a group of adult newly implanted recipients. Descriptive statistics specifically counts and percentages of device or procedure related adverse events will be summarized for the subject population.

The secondary endpoint will be assessed in the ITT analysis cohort with data through 6 months post-surgery.

6.6.3 Supporting Analyses

Additional supporting data collected in each cohort includes the following:

- Concomitant medications
- Bone conduction
- Sound field thresholds
- Speech perception testing in quiet and noise
- SSQ 12
- Patient Reported Questionnaire

6.7 Poolability Analyses

All investigational sites will follow the requirements of a common protocol and standardized data collection procedures and forms. The primary endpoints will be presented separately for each site using descriptive statistics. Poolability of the primary endpoint across investigational sites will be evaluated using a regression model with a fixed effect for site. Sites enrolling less than 3 subjects will be combined to form one-quasi site. If the quasi-site exceeds the maximum enrollment allowed per investigational site, centers will be combined based on geographical proximity to form multiple quasi-sites until at least 3 subjects are included in each quasi-site. 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.

6.8 Safety Analyses

Adverse events will be collected prospectively following implantation according to the Clinical Investigation Plan *A post-market interventional cohort study evaluating the clinical efficacy of the Osia 2 system in the US Market.* Descriptive statistics specifically counts and percentages of device or procedure related AEs will be summarized. Any subjects who die, are treatment failures, or discontinued an intervention due to an adverse event will be summarized separately.

Adverse events (AE) will be reported for the ITT population. 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) and will also be tabulated.

Device and procedure related AEs and SAEs, Adverse Device Effects (ADEs) and Serious Adverse Device Effects (SADEs), will also be summarized as described above. Unanticipated ADEs and SADEs (UADEs and USADEs) and adverse events leading to death or study discontinuation will be provided in listing format.

All device deficiencies will be reported in listing format.

6.9 Subgroup Analyses

Results for primary and secondary endpoints will be presented descriptively by sex and race.

6.10 Interim Analyses

No interim analyses are planned for this study.

6.11Protocol 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.

7 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.

8 Subject Listings

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