Cochlear®

QMS Document

For Internal Use Only

Statistical Analysis Plan

Clinical Investigation Plan (CIP) Title:	A Pre-Marketing, Prospective, Single-Site, Open-Label, Within-Subject, Feasibility, Interventional Study of Speech Perception with experienced adult cochlear implant recipients using the Nucleus 8 (CP1110) Sound Processor and compared with the Nucleus 7 (CP1000) Sound Processor.
CIP Number:	CLTD5804
CIP version:	V1.0, 13-APR-2021
Clinical Program Manager (CProM):	[redacted]

Contents

1 INTRODUCTION

This document is a companion document to the Clinical Investigation Plan (CIP). It includes a comprehensive description of the intended statistical analyses to be performed and the presentation of the results and data collected for the study.

This Statistical Analysis Plan (SAP) is based upon final CIP version 1.0, 13-APR-2021.

Any deviation from the Statistical Analysis Plan will be reported in the Clinical Investigation Report (CIR).

2 STUDY POPULATION

The subjects include men and women aged 18 years or older who are current users of a Nucleus 6 (CP910/920), Kanso (CP950) or Nucleus 7 (CP1000) Sound Processor. Subjects will be screened, and 20 eligible subjects will be recruited in the clinical investigation. For speech perception testing, all subjects will receive all treatment and control conditions; however, the test order will be counterbalanced/ randomised to control for order effects.

Subjects must meet all of the inclusion criteria described below to be eligible for this clinical investigation.

1) Aged 18 years or older
2) Post lingually deafened
3) Implanted with the CI600 Series (CI612, CI632, CI622, CI624), CI500 Series (CI512, CI532, CI522) or Freedom Series (CI24RE(CA), CI24RE(ST), CI422)
4) At least 6 months experience with a cochlear implant.
5) At least 3 months experience with a Nucleus 6 (CP910/920), Kanso (CP950), Kanso 2 (CP1150) or Nucleus 7 (CP1000) Sound Processor
6) Able to score 30% or more at +15 SNR with CI alone on a sentence in babble test
7) Willingness to participate in and to comply with all requirements of the protocol.
8) Fluent speaker in English as determined by the investigator
9) Willing and able to provide written informed consent

3 STUDY ENDPOINTS

For speech in noise (AuSTIN) endpoints, two lists of sentences will be measured per sound processor condition, and the two dB SRT values will be averaged to produce a single value per condition, per subject.

For speech in quiet (CNC) endpoints, two lists of words will be measured per sound processor condition, and the two percentage words correct values will be averaged to produce a single value per condition, per subject.

3.1.1 Primary Endpoint

The primary efficacy measure for the Nucleus 8 Sound processor will be Speech Reception Thresholds (SRT) assessed via AuSTIN Sentence scores in spatially separated adaptive noise.

The primary efficacy outcome for the study will be determined by the following primary efficacy endpoint:

- Paired difference in dB SRT (AuSTIN) between the Nucleus 8 Sound Processor with ForwardFocus On (BEAM) and the Nucleus 7 Sound Processor with ForwardFocus On (commercial version) (S0N90 4TB)

3.1.2 Secondary Endpoints

Secondary efficacy measures will be the percentage words correct as assessed by CNC (Consonant Nucleus Consonant) Monosyllabic word scores in quiet.

Secondary efficacy outcomes for will be determined by the following endpoints:

- Paired difference in percentage CNC Words correct in quiet (50 dB) with the Nucleus 8 Sound Processor (SNR-NR on) and Nucleus 7 Sound Processor (SNR-NR on)
- Paired difference in percentage CNC Words correct in quiet (50 dB) with the Nucleus 8 Sound Processor (Expander on) and Nucleus 7 Sound Processor (SNR-NR off)
- Paired difference in percentage CNC Words correct in quiet with the Nucleus 8 Sound Processor (Moderate) and Nucleus 7 Sound Processor (Standard directionality)

An additional secondary efficacy measure will be Speech Reception Thresholds (SRT) assessed via AuSTIN Sentence scores in spatially separated adaptive noise according to the following endpoint:

- Paired difference in dB SRT (AuSTIN) between the Nucleus 8 Sound Processor with ForwardFocus On (BEAM) and the Nucleus 7 Sound Processor with ForwardFocus On (commercial version) (S0N0 4TB)

3.1.3 Exploratory Endpoints

There are no exploratory endpoints

4 STATISTICS

4.1 Sample Size

This study is a non-inferiority design, and sample size calculation was based on non-inferiority tests for SRT (Speech Recognition Threshold) scores and CNC word scores. The sample size using a confidence interval method (one-tailed 97.5% confidence interval) was estimated to have a reasonable power to detect non-inferiority of sentence and word scores for the above-mentioned hypotheses.

To reject the null hypothesis of inferior sentence in noise scores (SRT scores), the following parameters for sample size calculation were chosen:

- A non-clinical important difference value of 1 dB SRT. This non-inferiority margin is based on clinical consensus that the SRT difference less than 1 dB between two sound processors is not regarded clinically significant. NB: *higher SRT scores represent poorer performance*.
- A standard deviation (SD) of change or difference scores of 1.36 dB. This SD is calculated from 256 paired differences and is an indicative test re-test SD for both S0N3 and S0N0.
- A significance level $\alpha = 0.025$ (one-tailed).

- A desired power of 0.8

Based on these assumptions, a sample size of 17 are required to reject the null hypotheses. Twenty subjects will be enrolled to allow for any unforeseen subject withdrawal.

4.2 Analyses

4.2.1 Pass/Fail Criteria

Not applicable

4.2.2 Primary Hypothesis

Endpoint: Paired difference in dB SRT (AuSTIN) between the Nucleus 8 Sound Processor with ForwardFocus On (BEAM) and the Nucleus 7 Sound Processor with ForwardFocus On (commercial version) (S0N90 4TB).

H0: Sentence in noise (S0N90 4TB) scores (dB SRT) with the Nucleus 8 Sound Processor with FF On (treatment) are inferior to those with the Nucleus 7 Sound Processor with FF On (control)

Nucleus 8 FF ON – Nucleus 7 FF ON ≥ 1 dB (NB: higher SRT scores represent poorer performance)

H1: Sentence in noise (S0N90 4TB) scores (dB SRT) with the Nucleus 8 Sound Processor with FF On (treatment) are non-inferior to those with the Nucleus 7 Sound Processor with FF On (control)

Nucleus 8 FF ON – Nucleus 7 FF ON < 1 dB

4.2.3 Secondary Hypotheses

Secondary endpoint 1

Paired difference in percentage CNC Words correct in quiet (50 dB) with the Nucleus 8 Sound Processor (SNR-NR on) and Nucleus 7 Sound Processor (SNR-NR on)

H0: Words in quiet (50 dB CNC words) scores (% words correct) with the Nucleus 8 Sound Processor SNR-NR on (treatment) are inferior to those with the Nucleus 7 Sound Processor SNR-NR on (control)

Nucleus 8 SNR-NR ON – Nucleus 7 SNR-NR ON $\leq$ -10%

H1: Words in quiet (50 dB CNC words) scores (% words correct) with the Nucleus 8 Sound Processor SNR-NR on (treatment) are non-inferior to those with the Nucleus 7 Sound Processor SNR-NR on (control)

Nucleus 8 SNR-NR ON – Nucleus 7 SNR-NR ON > -10%

Secondary endpoint 2

Paired difference in percentage CNC Words correct in quiet (50 dB) with the Nucleus 8 Sound Processor (Expander on) and Nucleus 7 Sound Processor (SNR-NR off)

H0: Words in quiet (50 dB CNC words) scores (% words correct) with the Nucleus 8 Sound Processor Expander on (treatment) are inferior to those with the Nucleus 7 Sound Processor SNR-NR off (control)

Nucleus 8 Expander On – Nucleus 7 SNR-NR off ≤ -10%

H1: Words in quiet (50 dB CNC words) scores (% words correct) with the Nucleus 8 Sound Processor Expander on (treatment) are non-inferior to those with the Nucleus 7 Sound Processor SNR-NR off (control)

Nucleus 8 Expander On – Nucleus 7 SNR-NR off > -10%

Secondary endpoint 3

Paired difference in percentage CNC Words correct in quiet with the Nucleus 8 Sound Processor (Moderate) and Nucleus 7 Sound Processor

H0: Words in quiet (50 dB CNC words) scores (% words correct) with the Nucleus 8 Sound Processor FF Moderate (treatment) are inferior to those with the Nucleus 7 Sound Processor std (control)

Nucleus 8 FF Moderate – Nucleus 7 std ≤ -10%

H1: Words in quiet (50 dB CNC words) scores (% words correct) with the Nucleus 8 Sound Processor FF Moderate (treatment) are non-inferior to those with the Nucleus 7 Sound Processor std (control)

Nucleus 8 FF Moderate – Nucleus 7 std > -10%

Secondary endpoint 4

Paired difference in dB SRT (AuSTIN) between the Nucleus 8 Sound Processor with ForwardFocus On (BEAM) and the Nucleus 7 Sound Processor with ForwardFocus On (commercial version) (S0N0 4TB).

H0: Sentence in noise (S0N0 4TB) scores (dB SRT) with the Nucleus 8 Sound Processor with FF On (treatment) are inferior to those with the Nucleus 7 Sound Processor with FF On (control)

Nucleus 8 FF ON – Nucleus 7 FF ON ≥ 1 dB (NB: higher SRT scores represent poorer performance)

H1: Sentence in noise (S0N0 4TB) scores (dB SRT) with the Nucleus 8 Sound Processor with FF On (treatment) are non-inferior to those with the Nucleus 7 Sound Processor with FF On (control)

Nucleus 8 FF ON – Nucleus 7 FF ON < 1 dB

4.3 Analysis Populations

4.3.1 Intent-to-Treat Population

The Intent-to-Treat analysis population will include all subjects who receive the treatments and have at least one set of paired treatment and control measurements from any endpoint, regardless of

protocol deviations and missing data. The Intent-to-Treat analysis population will provide supportive evidence to non-inferiority test, and will be the main analysis population for superiority test.

4.3.2 Per Protocol Population

The Per Protocol analysis population will include all subjects who receive the treatments and have at least one paired measurements from treatment and control, without major protocol deviations. Major deviations will be defined at the clean file meeting before data base lock. The Per Protocol analysis population will be the main analysis population for non-inferiority test.

It is possible that a treatment has not been administered in the intended counterbalanced order of presentation. It is also expected that the sequence and period effects are minimal in this study if any. This study is not a full cross-over design, so period and sequence effects will not be assessed in the main analysis, without the consequence to bias the study conclusion. The paired difference between Nucleus 8 Sound Processor and Nucleus 7 Sound Processor will also be estimated after accounting for period and sequence effects.

4.4 Additional Statistical Considerations

4.4.1 Missing, Unused or Spurious Data

See Section 4.3 for the intended treatment of missing or spurious data, such as CIP deviations.

4.4.2 Planned Interim Analysis

The sound quality reports and general feedback form study participants will be analysed on an ongoing basis and these will be used to improve the product. No formal interim analysis is planned for the speech perception assessments.

4.4.3 Criteria for Termination of the Clinical Investigation

The Sponsor will discontinue the clinical investigation site if:

1) major non-adherence to the CIP or GCP principles is occurring
2) it is anticipated that the subject recruitment will not be adequate to meet the objectives of the clinical investigation

An ongoing clinical investigation may be discontinued in case of:

1) device failure
2) serious or intolerable ADE, leading to the explant or discontinued use of the device
3) subject’s death

4.5 Conduct of Statistical Analysis

The statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released. Data will be listed and summarized using SAS® Version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina) per sponsor agreed reporting standards, where applicable.

Continuous data will be summarised using the Mean, Median, Standard Deviation (SD), Minimum (Min) and Maximum (Max) with the total number of subjects contributing values (N). Categorical measures will be summarised by presenting the number of subjects (N), count and percentage, as appropriate. Graphical presentation of the data will be performed as specified in the relevant sections.

SRT sentence scores and words in quiet scores at different speech testing conditions will be listed and summarised descriptively by treatment group and study population. A Scatter plot or similar plot will be used to present the individual data by treatment group, and bar chart will be used to present the average paired difference and its 95% CI.

For the non-inferiority test of SRT sentence scores for the primary and secondary endpoints, the 95% CI (alpha=0.025 one-sided) for the mean paired difference (treatment vs control) will be estimated. If the upper limit of the 95% CI of the mean paired difference is lower than 1dB, the treatment condition is regarded as non-inferior to the control in term of SRT sentence perception. The non-inferiority margin of 1dB for SRT is based on clinical consensus.

The same analysis method will be applied to the non-inferiority test for words in quiet scores (monosyllables). For the non-inferiority test of words in quiet scores, the 95% CI (alpha=0.025 one-sided) for the mean paired difference will be estimated. If the lower limit of the 95% CI of the mean paired difference is above -10%, the treatment condition is regarded as non-inferior to the control in term of words in quiet perception. The non-inferiority margin of -10% for words in quiet scores (monosyllables) is also based on clinical consensus.

Only when the non-inferiority test for the above specified endpoint is successful, then a superiority test for the endpoint will be further conducted to assess the treatment effect.

A paired t-test will be used to compare the above sound processor effect. While estimation of 95% CI of the paired difference is the main analysis method, an Analysis of Variance (ANOVA) approach will also be used to estimate the 95% CI of the paired difference, accounting for the cross-over design. The ANOVA model will account for the sequence and period effects when the sound processor effect is compared. The model takes the form:

SRT = test + sequence + subject (nested in sequence) + period

Sound processor effect estimated by the ANOVA model will be provided for comparison purpose, along with the results directly estimated by the paired data.

All demographics and baseline characteristics will be summarised descriptively. Any adverse events or device deficiencies will be listed in by-subject listings.

This is study is for product development. For each pre-planned comparison, a 95% CI of the comparison difference will be estimated, with type I error controlled at the significance level of 0.05 (two-sided) for each endpoint.

For regulatory purpose, a pre-specified hierarchy test will be used to control type I error in strong sense. For non-inferiority test, significance test for each endpoint will be assessed at the significance level of 0.05 (two-sided), in the pre-specified order from the primary endpoint to the secondary endpoint 4. Only if the first endpoint is significant, then the test can be carried out to the next

endpoint. Continue until the test for one endpoint in the sequence is not significant and stop further testing. All the following tests are regarded as exploratory and will not be used for decision-making.

4.6 Quality Control on Statistical Analysis

The study will be monitored for data quality, and adherence to ISO14155 and regulatory requirements.

4.7 Presentation of Data

Non-inferiority SRT data

Results will first be explained descriptively, outlining the mean value and standard deviation for both signal processing conditions, and the difference score and the 95% confidence interval of the difference scores.

Results from the non-inferiority comparing SRT scores for treatment and control will be presented graphically showing the group mean SRT performance for each signal processing setting and the 95% CI of the mean scores.

On a separate graph, the difference score will be plotted with the 95% confidence interval of the difference score relative to the non-inferiority margin to illustrate the hypothesis test in graph format.

Words in quiet data

Results will first be explained descriptively, outlining the mean value and standard deviation for both signal processing conditions, and the difference score and the 95% confidence interval of the difference scores

Results from the non-inferiority comparing CNC words scores for treatment and control will be presented graphically showing the group mean CNC words performance for each signal processing setting and the 95% CI of the mean scores.

On a separate graph, the difference score will be plotted with the 95% confidence interval of the difference score relative to the non-inferiority margin to illustrate the hypothesis test in graph format.

5 REFERENCES

5.1 Internal References

ID	Document Title	Number
1	Clinical Investigation Plan, V1.0, 13-APR-2021	VV-TMF-04139

5.2 External References

ID	Document Title	Number
NA		

6 CHANGE HISTORY

Version	Change	Author	Date
1.0	Introduction of the document	[redacted]	*refer to e-signature record*
2.0	Correction to hypothesis equations to be consistent with the hypothesis statements	[redacted]	*refer to e-signature record*

Signature Page for VV-TMF-05570 v2.0

Reason for signing: Approved	Name: [redacted] Role: A Date of signature: 12-Jan-2022 01:12:53 GMT+0000

Signature Page for VV-TMF-05570 v2.0