Cochlear®

QMS Document

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Statistical Analysis Plan

Clinical Investigation Plan (CIP) Title:	A Pre-Marketing, Prospective, Single-Site, Open-Label, Within-Subject, Pilot, Interventional Study of Adult Cochlear Implant Speech Perception with the Kanso 2 (CP1150) Sound Processor Compared with the Next Generation of Signal Processing Technology
CIP Number:	CLTD5818
Clinical Program Manager (CProM) or Statistician:	[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 on the approved CIP, document number VV-TMF-08761.

Any deviation from the Statistical Analysis Plan that occurs after database lock will be reported in the Clinical Investigation Report (CIR) providing a justification for the deviation.

1.1 Study Design

This is a pre-marketing, prospective, single-site, open-label, within-subject, pilot, interventional clinical investigation in adults with sensorineural hearing impairment who are current users of a Nucleus Cochlear Implant system.

After enrolment, subjects will attend a single study visit as described in the CIP Schedule of Events. At the study visit, subjects will undergo hearing assessments. Safety will be assessed by recording and summarising all Adverse Events (AE)/ Adverse Device Effects (ADE) and Device Deficiencies (DD). No data monitoring committee will be used for this clinical investigation.

Visit Type	Screening	Visit 1	EOS
Procedures			
Written informed consent	X		
Eligibility	X		
Sentence in babble test (+15 SNR)	X*		
Demographics	X		
Hearing history	X		
Device history	X		
Medical history	X		
Device fitting		X	
Speech perception testing – Words in Quiet 50 dB		X	
Concomitant medications/therapies		X	X
Adverse events		X	X
Device deficiencies		X	X
Device exposure		X	X

*If required

Design Rationale

Experienced adult cochlear implant recipients have been chosen as the study population due to their ability to compare Sound Processors across generations, in and outside of the booth. In addition, performance benefits achieved by adults can generally be extrapolated to younger age groups, avoiding the need to recruit this vulnerable population.

Comparison will be made within subjects with repeated measures for each of the sound processing conditions to be evaluated. There will be two test sessions with no take home use between sessions. The test sessions will include words in quiet tests. These speech measures are routine outcome measures used to evaluate new signal processing algorithms and hardware.

There will be no blinding of the study investigators.

Blinding of the study subject will be undertaken where possible, particularly when multiple signal processing conditions are loaded onto a single study device. Patients will not be told which program will be used in which order, and because the Kanso 2, Kanso 2 NF (Notch Filter) and Kanso 2 FF (ForwardFocus) Sound Processors are physically identical, it may also be possible to conceal which Sound Processor is being used during testing.

Counterbalancing of the test order will be undertaken where possible to limit the influence of order as described in Section 1.4.

1.2 Study Objectives and Endpoints

Primary Objective

To evaluate the impact of NF on adult cochlear implant recipient's speech perception in quiet using an off-the-ear (OTE) Sound Processor.

Secondary Objectives

- To evaluate the performance of FF combined with standard microphone directionality on adult cochlear implant recipient's speech perception in quiet using an OTE Sound Processor.
- To compare adult cochlear implant recipient's speech perception in quiet with Kanso 2 and Nucleus 8 Sound Processors

Exploratory Objective

To characterise the impact of NF on adult cochlear implant receipients, phoneme perception in quiet using an OTE (Kanso 2) Sound Processor.

1.3 Sample Size Justification

This study is a non-inferiority design, and sample size calculation was based on non-inferiority tests for CNC word scores. The sample size using a confidence interval method (two-tailed 95% confidence interval) was estimated to have a reasonable power to detect non-inferiority word scores for the listed hypotheses.

To reject the null hypothesis of inferior word perception in quiet for the new processor:

- A margin of non-inferiority of 10% has been chosen. That is, a true mean difference of up to -10% (defined as new-old) is acceptable and not considered a clinically meaningful change. This margin is based on clinical consensus, and previous feedback from the FDA.

- An expected standard deviation of difference scores of 7.5% for CNC words (50 dB), based on previous OTE studies investigating words in quiet.
- A significance level α = 0.05 (two-tailed).
- A desired power of 0.9.

Based on these assumptions, a sample size of 9 subjects is required to reject the null hypothesis. An increased sample size of 12 subjects will be enrolled, which will allow for the possibility that the variability in difference scores will be greater than expected and to account for the possibility of subject attrition.

1.4 Randomisation, Matching and Blinding

No treatment randomisation is planned. However, to control for order effects during speech perception testing for the Primary and Secondary Endpoints a 4x4 balanced Latin square order will be implemented (see table 3).

Table 3. Order of Administration of the Speech Perception Tests

	First Sound Processor	Second Sound Processor	Third Sound Processor	Fourth Sound Processor
SYD01, 05, 09	Kanso 2	Kanso 2 NF	Nucleus 8	Kanso 2 + FF
SYD02, 06, 10	Kanso 2 NF	Kanso 2 + FF	Kanso 2	Nucleus 8
SYD03, 07, 11	Kanso 2 + FF	Nucleus 8	Kanso 2 NF	Kanso 2
SYD04, 08, 12	Nucleus 8	Kanso 2	Kanso 2 + FF	Kanso 2 NF

For in booth speech perception testing, the test order will not be revealed to the study subject. The counterbalancing as outlined above will be used to ensure that there is a balanced order to the test conditions.

2 ENDPOINTS

2.1 Primary Endpoint

Paired difference in percentage CNC Words correct in quiet (50 dB) with the Kanso 2 NF and Kanso 2 (CP1150) Sound Processors

2.2 Secondary Endpoint(s)

- Paired difference in percentage CNC Words correct in quiet (50 dB) with the Kanso 2 FF (standard omni) and Kanso 2 (standard omni) Sound Processors
- Paired difference in percentage CNC Words correct in quiet (50 dB) with the Kanso 2 and Nucleus 8 Sound Processor.

2.3 Exploratory Endpoint(s)

Paired difference in percentage phonemes correct in quiet (50 dB) with the Kanso 2 NF and Kanso 2 Sound Processors

Control	Endpoint	Justification
Kanso 2 (CP1150) Sound Processor	**Primary Endpoints** Paired difference in percentage CNC Words correct in quiet (50 dB) with the Kanso 2 Sound Processor and Kanso 2 NF Sound Processor	**Input processing:** Standard microphone directionality + SNR-NR + subject's own MAP and ADRO/ASC preference Standard microphone directionality has been chosen to be consistent with the microphone directionality that SCAN+ selects in a quiet setting, and because the impact of the notch filters have the greatest potential for impact on speech in quiet.
Kanso 2 (CP1150) Sound Processor	**Secondary Endpoints** Paired difference in percentage CNC Words correct in quiet (50 dB) with the Kanso 2 Sound Processor and Kanso 2 Sound Processor with FF	**Input processing:** Standard microphone directionality + SNR-NR + subject's own MAP and Adaptive Dynamic Range Optimisation Autosensitivity (ADRO/ASC) preference Standard microphone directionality has been chosen to be consistent with the microphone directionality that SCAN+ selects in a quiet setting, and because the research question includes the performance of FF in a quiet scenario.
Nucleus 8 (CP1110) Sound Processor	**Secondary Endpoints** Paired difference in percentage CNC Words correct in quiet (50 dB) with the Kanso 2 Sound Processor and Nucleus 8 Sound Processor	**Input processing:** Standard microphone directionality + SNR-NR + subject's own MAP and ADRO/ASC preference Standard microphone directionality has been chosen to be consistent with the microphone directionality that SCAN+ selects in a quiet setting
Kanso 2 (CP1150) Sound Processor	**Exploratory Endpoint** Paired difference in percentage phonemes correct in quiet (50 dB) with the Kanso 2 Sound Processor and Kanso 2 NF Sound Processor	See primary endpoint justification

2.4 Safety Endpoint(s)

There are no specified safety endpoints. See section 8.2 for the methods to analyse safety data.

3 Hypothesis and Decision Rules

For the non-inferiority test of CNC word score, the 95% CI (alpha=0.025 one-sided) for the mean paired difference (Kanso 2 NF versus Kanso 2 (no notch filters or standard omni) for the primary endpoint, Kanso 2 (no notch filters or standard omni) + ForwardFocus (standard omni) versus Kanso 2 (no notch filters and standard omni) and Kanso 2 (no notch filters or standard omni) versus Nucleus

8, respectively for the secondary endpoints) will be estimated. If the lower limit of the 95% CI of the mean paired difference is above -10%, the 'experimental SP' (Kanso 2 NF, Kanso 2 [no notch filters] + ForwardFocus [standard omni], and Kanso 2 [no notch filters or standard omni], respectively for the primary and secondary endpoints) is regarded as non-inferior to the 'control SP' on that measure.

3.1 Statistical Hypothesis

3.1.1 Pass/Fail Criteria

See hypotheses.

3.1.2 Primary Hypothesis

Endpoint: Paired difference in percentage CNC Words correct in quiet (50 dB) with the Kanso 2 (notch filters) and Kanso 2 (no notch filters) Sound Processors; higher score corresponds with a better outcome.

H0: Words in quiet (50 dB CNC words) scores (% words correct) with the Kanso 2 NF Sound Processor (treatment) are inferior to those with the Kanso 2 Sound Processor (control)

Kanso 2 NF – Kanso 2 $\leq$ -10%

H1: Words in quiet (50 dB CNC words) scores (% words correct) with the Kanso 2 NF Sound Processor (treatment) are non-inferior to those with the Kanso 2 Sound Processor SNR-NR on (control)

Kanso 2 NF – Kanso 2 > -10%

3.1.3 Secondary Hypotheses

Endpoint: Paired difference in percentage CNC Words correct in quiet (50 dB) with the Kanso 2 + FF (standard omni) and Kanso 2 (standard omni) Sound Processors

H0: Words in quiet (50 dB CNC words) scores (% words correct) with the Kanso 2 FF Sound Processor (standard omni) (treatment) are inferior to those with the Kanso 2 Sound Processor (standard omni) (control)

Kanso 2 FF – Kanso 2 $\leq$ -10%

H1: Words in quiet (50 dB CNC words) scores (% words correct) with the Kanso 2 FF Sound Processor (treatment) are non-inferior to those with the Kanso 2 Sound Processor (standard omni) (control)

Kanso 2 FF – Kanso 2 > -10%

Endpoint: Paired difference in percentage CNC Words correct in quiet (50 dB) with the Kanso 2 and Nucleus 8 Sound Processors

H0: Words in quiet (50 dB CNC words) scores (% words correct) with the Kanso 2 sound processor (treatment) are inferior to those with the Nucleus 8 Sound Processor (control)

Kanso 2 – Nucleus 8 $\leq$ -10%

H1: Words in quiet (50 dB CNC words) scores (% words correct) with the Kanso 2 sound processor (treatment) are non-inferior to those with the Nucleus 8 Sound Processor SNR-NR on (control)

Kanso 2 – Nucleus 8> -10%

3.2 Statistical Decision Rules

No adjustments will be made for multiplicity of testing. All p-values reported will be at the nominal 5% significance level.

4 INTERIM ANALYSES, UNBLINDING AND INDEPENDENT DATA MONITORING COMMITTEE REVIEW

4.1 Interim Analyses and Unblinding

Not applicable

4.2 Independent Data Monitoring Committee Review

Not applicable

5 ANALYSIS POPULATIONS

This study has a non-inferiority design; therefore, the primary analysis will be based on the PP population. If non-inferiority is demonstrated, the test of superiority in the Per Protocol (PP) and the Intent-To-Treat (ITT) analysis sets will follow.

For cases in which the ITT and PP populations lead to the same conclusions and final interpretations about the treatment effect, the results will be considered to not be influenced by underlying factors such as missing data and protocol deviations, and the results would be considered to be robust and consistent under different analysis populations. A statement to reflect this will be included in the CIR.

For cases in which the ITT and PP populations lead to different final interpretations or conclusions, the results will be reported for both analysis sets and the differences in outcomes will be identified and explored.

5.1 Intent-to-Treat Analysis Set

The Intent-to-Treat 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.

5.2 Per Protocol Analysis Set

The Per Protocol Population will include all subjects who receive the treatments and have at least one paired measurement from treatment and control, without major protocol deviations. Major deviations will be defined at the clean file meeting before data base lock.

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 likely to be negligible in this study.

5.3 Safety Analysis Set

The Safety Population will include all treated subjects. The Safety Population will be used for the safety data analysis.

5.4 Other Analysis Sets

Not applicable

5.5 Misallocations to Treatment

Not applicable

5.6 Protocol Deviations

Major protocol deviations will be listed for the safety population with the reason(s) for the deviation(s). Major deviations will include violations of eligibility criteria, incorrect order of administration of the SPs, or an incorrect administration of a test condition.

6 ADDITIONAL STATISTICAL CONSIDERATIONS

6.1 Descriptive Statistics and General Analyses Methods

All data collected will be listed. Continuous data will be described by the number of non-missing observations, mean, median, minimum value, maximum value and the standard deviation. Categorical data will be summarised by the number and proportion in each category. Confidence intervals will be two-sided and at the 95% confidence level. Figures as appropriate to further describe the data may be presented.

See Section 8for further information of statistical analysis.

6.2 Missing, Unused or Spurious Data

Missing data will not be imputed.

6.3 Visit Windows

This is a single visit study with no visit windows applicable.

6.4 Imputation of Partial Dates

This is a study conducted at a single visit. There are no outcomes that are time dependent to be reported.

6.5 Covariates

Not applicable

6.6 Subgroup Analyses

No subgroup analyses are planned.

6.7 Additional Statistical Analyses

Not applicable

7 SUBJECT INFORMATION

Demographic and baseline Characteristics

Demographic and baseline characteristics collected in this study will be summarised appropriately for the safety population. Baseline characteristics will include summaries of hearing history, device history (hearing aid and implant), medical history and medications commenced prior to screening.

Subject Disposition

Subject disposition will be summarised with reasons for discontinuation for the safety population. Additionally, the reason for exclusion from the per-protocol population will also be presented with details of the deviations.

Extent of Exposure and Duration of Follow-Up

The study is a single visit study, with up to 3 hours of testing per subject. Any deviations from this plan will be listed in the clinical investigation report.

Protocol Deviations

Major protocol deviations will be listed for the safety population with the reason(s) for the deviation(s).

Concomitant Medications

Concomitant medications received during the study will be summarised appropriately for the safety population.

8 STATISTICAL ANALYSES

8.1 Efficacy Analysis

Primary and Secondary Speech Perception Endpoints:

Words in quiet scores at different speech testing conditions will be listed and summarised descriptively by treatment group and study population. Figures as appropriate to further describe the data may be presented.

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.

While sequence and period effects are expected to be minimal in this single day, in booth study of approximately 3 hours duration, an analysis of variance (ANOVA) that considers the sequence and period effects will also be conducted as a supportive analysis to the paired t-test. The model will be formulated as follows:

CNC words in quiet (% correct) = device + period + sequence + subject (nested in sequence)

The least squares mean difference in CNC words (in quiet) estimated by the ANOVA model will be provided along with a 95% confidence interval.

If non-inferiority is demonstrated, the testing will proceed to a test of superiority.

These results will also be presented graphically illustrating the observed mean, its 95% CI and the non-inferiority margin as defined by the hypothesis test.

8.2 Safety Analysis

Incidence of adverse events (AE/ADE) will be presented. Additionally, the severity, relationship to treatment, outcome and actions taken will be listed for each subject. Likewise, the devices deficiencies (DD) will also be reported as incidences and listed.

For AE/ADEs and DDs, the percentage of subjects who experienced at least one occurrence of each, will be summarised. Any subjects who died, who discontinued an intervention due to an AE/ADEs, or who experienced a severe or an SAE/SADEs will be summarised separately.

8.3 Other Analyses

Not applicable

9 References

9.1 Internal References

ID	Document Title	Number
CLTD5818 CIP	CLTD5818 Clinical Investigation Plan	VV-TMF-08761

9.2 External References

ID	Document Title	Number
Not applicable	Not applicable	Not applicable

10 Change History

Version	Change	Author	Date
1.0	Introduction of the document	[redacted]	*refer to e-signature record*

11 DEFINITIONS

Term	Description
CIP	Clinical Investigation Plan
SAP	Statistical Analysis Plan
AE	Adverse Event
ADE	Adverse Device Effect
DD	Device Deficiency
NF	Notch Filter
FF	ForwardFocus
OTE	Off-the-ear sound processor
CNC	Consonant Nucleus Consonant speech test
SNR-NR	Single to noise ratio noise reduction
ADRO/ASC	Adaptive dynamic range optimisation and autosensitivity
SP	Sound Processor
ITT	Intent-to-treat
PP	Per Protocol
CI	Confidence interval
ANOVA	Analysis of variance
SAE/SADEs	Serious Adverse Event/Serious Adverse Device Effect

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