STATISTICAL ANALYSIS PLAN

Front-End Processing 3.0 - Noise reduction, Transient Reduction, Scene Classifier

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VERSION HISTORY

This list includes all previous versions of the document, including the version number, the date the SAP became effective, as well as a short description of changes to previous versions.

Version no°	Effective Date	Description of Changes
1.0	19 FEB 2020	Document generated

1 ABBREVIATIONS

Terms used in this document refer to SOP [redacted] The following terms are specific to this document:

Abbreviation	Definition
ACALES	Adaptive Categorical Listening Effort Scaling
AE	Adverse Event
APSQ	Audio Processor Satisfaction Questionnaire
ASC	Automatic Scene Classifier
ASM	Automatic Sound Management
CI	Cochlear Implant
CIP	Clinical Investigation Plan
CRF	Case Report Form
CRM	Clinical Research Manager
DMP	Data Management Plan
FEP	Front-end Processing
HISQUI	Hearing Implant Sound Quality Index
ICF	Informed Consent Form
MP	Monitoring Plan
NR	Noise Reduction
OLSA	Oldenburger Sentence Test (Oldenburger Satztest)

PP	Per Protocol
PTA	Pure Tone Audiometry
SAP	Statistical Analysis Plan
SD	Standard Deviation
SNR	Signal-to-Noise Ratio
SPL	Sound Pressure Level
SRT	Speech Reception Threshold
SSQ12	The Speech, Spatial and Qualities of Hearing Scale (short version with 12 questions)
TR	Transient Noise Reduction
VAS	Visual Analogue Scale
WNR	Wind Noise Reduction

2 DEVELOPMENT OF THE SAP

Recommendations of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) based on ICH E9 (Statistical Principles for Clinical Trials) with references to ICH E3 (Structure and Content of Clinical Study Reports) are incorporated in the SAP.

3 GOALS OF THE SAP

The SAP is intended to be a comprehensive and detailed description of the methods and presentation of data analysis proposed for a clinical investigation, to avoid post hoc decisions that may affect the interpretation of the statistical analysis.

4 INTRODUCTION

4.1 Preface

MED-EL Cochlear Implants (CI) provide auditory sensations via electrical stimulation of the auditory pathways for severely to profoundly hearing-impaired individuals who obtain little or no benefit from acoustic amplification in the best aided condition. Front-end processing of acoustic signals picked up by the audio processor is routinely applied to provide optimal hearing performance under varying listening conditions. Automatic Sound Management (ASM) was introduced by MED-EL with the TEMPO+ audio processor and provided advanced compression and automatic gain management. With the SONNET audio processor MED-EL introduced ASM 2.0 which added wind noise reduction and microphone directionality to the front-end processing. With the new SONNET 2 audio processor, ASM 3.0 was implemented and the features noise reduction, transient reduction and an automatic scene classifier were added.

4.2 Purpose of the Analyses

This study will investigate the impact of ASM 3.0 as implemented in the SONNET 2 on CI users' speech performance and their subjective quality of hearing.

5 STUDY OBJECTIVES

5.1 Primary Objective

- Comparison between the speech reception thresholds in the OLSA test in noise (S0N0) of the SONNET 2 programmed as a SONNET and the SONNET 2 (setting 1; ASC off, mild WNR, mild NR, mild TR).

5.2 Secondary Objectives

- Comparison between the speech reception thresholds in the OLSA test in noise across all audio processors and audio processor settings.
- Comparison between the speech reception in quiet (Freiburg Monosyllables Test) across all audio processors and audio processor settings.
- Comparison of subjective user satisfaction, sound quality, quality of hearing, and listening effort across audio processors and audio processor settings.

6 STUDY OUTCOME MEASURES (ENDPOINTS)

6.1 Primary Outcome Measure

The primary outcome measure is speech intelligibility in the S0N0 set-up in the OLSA speech test in noise (as dB SNR).

6.2 Secondary Outcome Measures

Performance of the SONNET 2 will be assessed with different combinations of frontend processing features under different environmental test conditions using the following tests:

- Speech performance
    - Freiburg Monosyllabic test in quiet; speech presented from the front
    - Oldenburg Sentence Test in noise in the set-ups:
        - ⇒ S0N0
        - ⇒ S0N0T0
        - ⇒ S0, ±N45, ± N135
- Quality of hearing in real life
    - HISQUI19
    - SSQ12
- Device handling
    - Data Logging
    - APSQ
- Subjective Rating
    - ACALES
    - Subjective Sound Quality Rating
    - Product Specific Questionnaire

7 STUDY METHODS

7.1 Type of Study / Study Design

This study has been planned as a mono-centric, open label, prospective longitudinal study where each subject acts as his/her own control.

The SONNET 2 is an incremental innovation to the SONNET audio processor with additional front-end processing features which are designed to improve patient performance in specific auditory environments. The study is designed to prospectively follow-up experienced SONNET users who received the SONNET 2. As intra-individual control, subjects will be acutely tested with the SONNET in the same test conditions as with the SONNET 2.

7.2 Study Population

This study will be performed with experienced users of MED-EL cochlear implants (defined as a minimum experience of 6 months with a MED-EL cochlear implant and their current audio processor) who will be followed-up for five study specific visits at the test centre.

7.3 Study Duration / Enrolment Period

This study is expected to be active for 15 months. This consists of an enrolment period of 12 months and a maximum participation of an individual subject for 3 months.

7.4 Selection Criteria

7.4.1 Inclusion criteria

- A minimum of 18 years old
- Experienced user (≥ 6 months) of a MED-EL cochlear implant (C40+ and later model)
- Experienced user (≥ 6 months) of a MED-EL SONNET audio processor
- Post-lingual onset of bilateral severe to profound sensory-neural hearing loss
- Unilateral CI user
- A minimum of 10 active electrodes
- A minimum of 40% speech recognition in the Freiburg Monosyllables test in quiet at 65 dB SPL (at the last time tested)
- Fluent in German (the language of the test centre)

- Signed and dated ICF before the start of any study-specific procedure.

7.4.2 Exclusion criteria

- Lack of compliance with any inclusion criteria
- CI user with contralateral hearing equal to or better than 60 dB (PTA measured at 500, 1000, and 2000Hz))
- EAS user (user of an EAS audio processor)
- Implanted with C40X and C40C
- Implanted with an ABI or Split electrode array
- Known allergic reactions to components of the investigational medical device
- Unstable psychological status
- Anything that, in the opinion of the Investigator, would place the subject at increased risk or preclude the subject's full compliance with or completion of the study

7.5 Randomization and Blinding

The order of the audio processor testing will be randomised for each subject and study visit. Additionally, it will be randomised which audio processor configurations will be taken home after a particular visit. These randomizations will be performed to avoid any sequence-effects (e.g. training effect, fatigue effect). The particular fitting configuration and the order of the test procedures is verbally stated in the respective CRFs for each subject and each study visit.

Details on randomization can be found in the Data Management Plan (DMP).

7.6 Tests / Study Variables

Audio Processor	Configuration	**Visit 1**	**Visit 2[1]**	**Visit 3[1]**	**Visit 4[1]**	**Visit 5[1]**
		Speech in quiet (S0)	Speech in noise (S0N0 & S0N0T0)	Speech in noise (S0 ±N45 ±N135)	Subjective ratings	Subjective ratings
SONNET	Default SONNET	✓	✓	✓	x	x
SONNET 2	OPUS 2	✓	✓	✓	✓	✓
SONNET 2	Default SONNET	✓	✓	✓	✓	✓
SONNET 2	SONNET 2/ Configuration 1[2]	✓	✓	✓	✓	✓
SONNET 2	SONNET 2 Configuration 2[2]	✓	✓	✓	✓	✓
SONNET 2	SONNET 2 Configuration 3[2]	✓	✓	✓	x	x
SONNET 2	SONNET 2/ Configuration 4[2]	✓	✓	✓	x	x
Questionnaires		SONNET: APSQ HISQUI SSQ	SONNET 2: SONNET 2[3] Questionnaire HISQUI SSQ	SONNET 2: SONNET 2[3] Questionnaire APSQ HISQUI SSQ	SONNET 2: SONNET 2[3] Questionnaire HISQUI SSQ	SONNET 2: SONNET 2[3] Questionnaire HISQUI SSQ

Take home 2 programs

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1 Study Visit is conducted 2 weeks (±1 week) after the previous visit
2 Details on all SONNET 2 configurations are described in the CIP
3 The questionnaire will be completed for the SONNET 2 in the SONNET default configuration and one of the four SONNET 2 configurations (which will be randomised across subjects).

7.6.1 Speech testing in quiet

The Freiburg Monosyllabic Word test evaluates the number of correctly repeated words in % correct at a fixed presentation level.

7.6.2 Speech testing in noise

The OLSA test is used to assess the speech-recognition threshold for 80% correct word recognition in noise (SRT80 in dB SNR). The noise level is fixed, and the speech level is adaptive.

7.6.3 Subjective ratings

7.6.3.1 Subjective sound

Subjective sound quality ratings of the different SONNET 2 configurations will be assessed on a visual analogue scale (VAS) for a range of signals comprising different samples of speech, music, and background noises. The subject will rate the perceived quality on different scales compared to a reference condition.

7.6.3.2 ACALES Test

In this test, the subject will listen to speech in noise and will rate the subjectively perceived listening effort on a scale from "effortless" to "extremely effortful". Depending on the rating of the subject, the level of the speaker will be varied adaptively while the noise level is kept constant. This test will be performed in different fitting configurations and test set-ups

7.6.4 Questionnaires

7.6.4.1 Audio Processor Satisfaction Questionnaire (APSQ)

The APSQ is a validated general questionnaire which is designed to assess the handling of MED-EL devices. It assesses the wearing comfort, sound quality, and other device-specific factors related to the audio processor with 15 items on a VAS scale from 0 ('does not agree at all') to 10 ('fully agrees'). If an item does not apply to the subject, then the subject can tick the 'not applicable' option. The maximum number of incomplete answers for the validation analyses is set at three items per subject; if this number exceeds, then the subject shall be excluded.

7.6.4.2 *Hearing Implant Sound Quality Index 19 (HISQUI19)*

The questionnaire consists of 19 seven-level Likert items ranging from ´always = 7` to ´never =1`. Added percentage values support the answering of the items. The total score is the sum of all items and ranges from 19 to 133 points. Missing data and the answer option ´not applicable` (N/A) are treated as ´missing values`. The maximum number of incomplete answers are set at three items per subject; if this number exceeds the subject shall be excluded.

7.6.4.3 *SSQ12 (Speech Spatial Qualities) in German*

The SSQ questionnaire (Noble et al. 2013) is a sensitive and specific measure to assess the impact of hearing loss on speech perception, sound localization, and QoL. The SSQ12 consists of 12 questions that the subjects score on a scale from 0 (not at all) to 10 (perfectly). The total score is the sum of all items and can range between 0 and 120. The items can also be classified into the following subscores:

- Speech: Items 1 -5
- Spatial: Items 6 – 8
- Qualities: Items 9 – 12

Scoring rules:

- Questions answered with "not applicable" (N/A) or not answered are rated as missing value.
- The maximum number of incomplete answers will be set at 2 items per subject; if this number exceeds the subject will be excluded.
- The results of the questions can be added up totally or within the subgroups listed above.

7.6.4.4 *SONNET 2 questionnaire*

A study specific questionnaire was developed to compare the four new SONNET 2 fitting configurations to the previous SONNET settings. The questionnaire covers different everyday situations (e.g. conversations in a cocktail party setting, speech different background noise situations, music etc.). The subjects are asked to state which fitting configuration they prefer and to give a reason why. Additionally, there are blank spaces where each subject can state situations which are important to them, they can state their preferred fitting and also tick why a particular fitting was preferred. Missing data are treated as missing values.

8 SAMPLE SIZE

The primary objective of this study is to show non-inferiority of SONNET2 in a OLSA in noise speech test (S0N0) compared to the SONNET. The margin of non-inferiority is set to 2 dB SNR.

Comparable data of the final report "Performance of Cochlear Implant Patients with Microphone Directionality and Wind Noise Reduction with the "SONNET" of the OLSA in noise speech test (S0N0) were used as basis for the sample size calculation:

OPUS2	mean: 0.589 dB;	± SD: 1.586 dB vs.
SONNET natural-MILD	mean: -0.088 dB;	± SD: 1.463 dB

The sample size was estimated using the formula on noninferiority (Chow, Shao et al. 2008):

$$N = (1 + \frac{1}{r})(\sigma \frac{Zcrit + Zpwr}{(\mu A - \mu B) - \Delta})^2$$

Assuming a non-inferiority margin of 2 dB (Δ), with an alpha-level of 0.025 (noninferiority, one-sided) and a power of 90%, a minimum sample size of 13 subjects was calculated (Zcrit is the normal quantile for the 0.025 alpha level, and Zpwr is the normal quantile for the 90% power). To allow for possible dropouts (approximately 20%) and to provide additional safety and efficacy data, a maximum of 30 subjects will be included in this study.

9 HYPOTHESES

9.1 Hypothesis for the Primary Objective

The primary objective of this study is to show non-inferiority of SONNET2 in a OLSA in noise speech test (S0N0) compared to the SONNET. The margin of non-inferiority is set to 2 dB SNR.

- Verbal formulation

Hypothesis H_0 (Null Hypothesis):

Speech perception with the SONNET 2 in its default setting in the OLSA in noise (S0N0) is inferior to the speech perception in the same test condition with the SONNET. A mean difference of ≥ 2 dB is considered as a clinically relevant difference.

Hypothesis H_1 (Alternative Hypothesis):

Speech perception with the SONNET 2 in its default setting in the OLSA in noise (S0N0) is non-inferior to the speech perception in the same test condition with the SONNET. A mean difference of less than 2 dB is not considered as a clinically relevant difference.

- Mathematical formulation

H_0: $\mu 1 - \mu 2 \geq \Delta$ (2 dB SNR)

H_1: $\mu 1 - \mu 2 < \Delta$ (2 dB SNR)

Where: μ_1 = mean OLSA in noise (S0N0) results as dB SNR with the SONNET

μ_2 = mean OLSA in noise (S0N0) results as dB SNR with the SONNET2

9.2 Hypotheses for the Secondary Objectives

The secondary objectives of this study are to provide additional evidence on the performance of SONNET 2-specific front-end features. Thus, the analyses are of an explorative nature and will not influence the results of the primary outcome of the study. Due to the exploratory nature of the secondary objectives, no hypotheses are formulated a priori.

10 GENERAL CONSIDERATIONS

10.1 Timing of Analyses

The final analysis will be performed when all enrolled subjects have finished the last study visit. No interim analysis is planned.

10.2 Analysis Population

The Per Protocol Analysis (PP) will include all patients who adhere to the major criteria of the protocol; otherwise that patient will be excluded from the analysis.

11 STATISTICAL ANALYSIS METHODS

11.1 Descriptive Statistics

Descriptive statistics will be applied to describe patient characteristics (e.g. age, gender, aetiologies) and the examined study outcomes. For quantitative data the mean, the standard deviation (SD), and/or the median with range (minimum and maximum values) will be calculated. For qualitative data absolute and relative frequencies will be used.

The number (n) and the percentage (%) of AEs will be recorded according to causality as defined in the CIP.

11.2 Inferential Statistics

11.2.1 Primary Objectives

The mean difference (dB SNR) with the 95% confidence intervals of the OLSA in noise speech test (S0N0) between the SONNET and the SONNET2 will be calculated to examine if the mean difference lies below the a-priory specified non-inferiority margin of 2 dB.

11.2.2 Secondary Objectives

The secondary objectives of this study are of an explorative nature and provide additional evidence on the performance of SONNET 2-specific front-end features. The performance of the SONNET 2 will be assessed with different combinations of frontend processing features under different environmental test conditions using the following tests:

- Speech performance
    - Freiburg Monosyllabic test in quiet; speech presented from the front
    - Oldenburg Sentence Test in noise in the set-ups:
        - ⇒ S0N0
        - ⇒ S0N0T0
        - ⇒ S0, ±N45, ± N135
- Quality of hearing in real life
    - HISQUI19
    - SSQ12
- Device handling

- Data Logging
- APSQ

- Subjective Rating
  - ACALES
  - Subjective Sound Quality Rating
  - Product Specific Questionnaire

The Kolmogorov-Smirnov test, the Shapiro-Wilk test and a graphical examination will be conducted in a first step to check the data distribution of the secondary endpoints. Based on the data parametric and/or non-parametric tests such as the Paired sample t-test or the Wilcoxon signed-rank test will be applied.

12 Data Handling

12.1 Reporting of Significance Level

Statistical significance is set to $p \leq 0.05$. The corresponding confidence level is 95%.

12.1.1 Multiplicity Adjustment

The problem of multiplicity (i.e. to avoid the Type I error) resulting of multiple comparisons will be solved by adjusting the p-values using the Holm-Bonferroni correction method.

12.2 Handling of Missing Data

Missing data will be treated as missing values.

12.3 Presentation of Data

The results of the data analyses may be presented in tables and/or displayed in graphs depending on their nature and meaning.

13 PROTOCOL DEVIATIONS

Protocol deviations that could impact the statistical analysis shall be discussed with the Clinical Research Manager as well as with the Study Monitor and the Data Manager. If applicable, the methods used to analyse them shall be specified and reported in the "Final Study Report".

14 VALIDITY

14.1 Internal Validity

Following procedures to gain internal validity have to be done:

- The study is monitored according to the Monitoring Plan.
- Data transferred from the CRFs to the study database is validated according to the Data Management Plan (DMP).

15 DOCUMENTATION OF DATA HANDLING AND TRANSFER

Details on documentation and handling of data can be found in the DMP.

17 POST-ANALYSIS QUALITY CONTROL

The results of the data analysis performed by the MED-EL Statistician will be validated by a reviewer and a Statistical Analysis Validation Report will be issued. The results of the data analysis and the validation report will be reviewed by the Study Manager and the Study Monitor of the study.

18 REFERENCES

Chow, S.-C., et al. (2008). Sample size calculations in clinical research. Boca Raton, Chapman & Hall/CRC.