Statistical Analysis Plan

FINAL

Cochlear Baha Attract System

CBAS5477

Post-market clinical follow-up of a magnetic bone conduction implant

A multicentre, open, prospective clinical investigation. 6 months investigation with an 18 months follow-up period.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADE	Adverse Device Effect
AE	Adverse Event
APHAB	Abbreviated Profile of Hearing Aid Benefit
ATC	Anatomic Therapeutic Chemical classification system
BC	Bone Conduction
BFS	Baha Fitting Software
cm	Centimetre
d	Day
dB	Decibel
DD	Device Deficiency
HUI	Health Utility Index
Hz	Hertz
in	Inch
ITT	Intention to treat
kg	Kilogram
KM	Kaplan-Meier
lbs	Pounds
m	Month
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
min	Minute
Min	Minimum
mm	Millimetre
PL	Poland
PP	Per protocol
PT	Preferred Term
PTA	Pure Tone Average
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SEM	Standard Error of the Mean
SOC	System Organ Class
SP	Sound Processor
SPM	Sound Processor Magnet
SSD	Single Sided Deafness
SSQ	The Speech, Spatial and Qualities of Hearing Scale
UK	United Kingdom
USA	United States of America
w	Week
WHO CC	World Health Organization Collaborating Centre for Drug Statistics Methodology

1 STUDY DETAILS

1.1 Study Objectives

1.1.1 Primary objective

To compare the hearing performance with the Baha Attract System (aided) and the unaided hearing performance.

1.1.2 Secondary objectives

- To compare the hearing performance with the Baha Attract System and the hearing performance with the same sound processor on a Baha Softband.
- To compare health status, health-related quality of life and utility scores before and after use of the Baha Attract System.
- To compare the self-reported assessment of hearing aid outcome before and after use of the Baha Attract System.
- To collect surgical information.
- To investigate if the Sound Processor Magnet strength and magnetic force required for retention changes over time.
- To collect information regarding pain, discomfort, numbness and soft tissue status.
- To monitor implant survival.
- To collect Adverse Events and device deficiencies.

1.2 Study Design

This investigation is a multicentre, open, prospective clinical investigation with only one device group. It is a 6 months investigation with an 18 months follow-up period.

1.2.1 Flowchart

Procedures and timing	**Visit 1** Softband test	**Visit 2** Surgery	**Visit 3** Suture removal	**Visit 4** Fitting	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8 ***	**Visit 9 ***
Day/Week/Month[1]	**Pre-op**	**D 0**	**D 10**	**W 4**	**W 6**	**W 12**	**M 6**	**M 12**	**M 24**
Time window			± 5d	± 1w	± 1w	± 2w	± 4w	± 4w	± 4w
Demographics	X								
Medical history	X								
Nicotine use	X								
Audiogram[2]	X								X
Eligibility criteria	X								
Informed consent	X								
Soft tissue thickness	X	***or*** X							
Health Utility Index (HUI)[3]	X[4]						X		X
Abbreviated Profile of Hearing Aid Benefit (APHAB)[3]	X[4,5]						X[6]		X[6]
The Speech, Spatial and Qualities of Hearing Scale (SSQ)[3]	X[4,5]						X[6]		X[6]
BC Direct using BFS	X[7]			X[8]					X[9]
Selection of sound processor	X								
Change of sound processor				X[9]	X[9]	X[9]	X[9]	X[9]	X[9]
Fitting of sound processor	X[7]			X[8]					X[9]
Fine tuning of sound processor					X[9]	X[9]	X[9]	X[9]	X[9]
Free field thresholds	X[5,7]			X[8]			X[8]	X[8]	X[8]
Speech recognition in noise	X[5,7]			X[8]			X[8]	X[8]	X[8]
Speech recognition in quiet	X[5,7]			X[8]			X[8]	X[8]	X[8]
Home test of sound processor on Softband	X →								
Surgery		X							
Surgery time		X							
Soft tissue thinning		X							
Bone polishing/removal		X							
Implant stability quotient		X							
Suture removal (if applicable)			X						
SP Magnet selection				X					
Magnetic retention force				X	X	X	X	X	X
Change of SP Magnet					X[9]	X[9]	X[9]	X[9]	X[9]
Questions regarding: • Daily use of sound processor • Magnet retention • Change of soft pad					X	X	X	X	X
Pain/discomfort					X	X	X	X	X
Numbness			X	X	X	X	X	X	X
Soft tissue status			X	X	X	X	X	X	X
Loss/removal of Implant or Implant Magnet			X	X	X	X	X	X	X

Device deficiency		X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X
Concomitant medication/treatment	X	X	X	X	X	X	X	X	X
Extra visit									
Extra visit									

*[1] The time between visits was calculated from Visit 2 (time 0); [2] Only if the last audiogram that was performed on the subject was older than 6 months; [3] To be completed by the subject; [4] Before Softband test; [5] Unaided; [6] Aided; [7] With sound processor on Softband; [8] With Baha Attract System; [9] If needed; * Visit 8 and 9 are not included in the sixth months analysis*

1.3 Device/Treatment Groups

Only one device group is included in this study.

1.4 Sample Size

1.4.1 Sample size calculation for the primary efficacy analysis:

In order to achieve 90 % power to detect a clinically significant difference of 10 dB in free-field hearing thresholds between the unaided situation and the Baha Attract System at the 6 months visit with Fisher's non-parametric permutation test for paired observation, two-sided test with significance level 0.05, on the ITT population 20 evaluable subjects are needed assuming a within subject standard deviation (SD) of 13.0 dB. The within subject SD for change in PTA4 has been estimated to 12.3 dB in a previous study within Cochlear comparing unaided hearing with a BP100 sound processor on a Cochlear Baha Attract System, CBAS5477 42 (51) Softband versus unaided hearing. To compensate for a 10% drop out rate in the study 22 subjects should be included in the investigation.

1.4.2 Sample size calculation for the for the secondary analysis

In order to achieve 90 % power to detect a clinically significant change of 1.5 dB in free-field hearing thresholds from Softband to the Baha Attract System at the 6 months visit with Fisher's non-parametric permutation test for paired observation, two-sided test with significance level 0.05, on the ITT population 46 evaluable subjects are needed assuming a within subject SD of 3 dB. The within subject SD for change in PTA4 has been estimated to 2.89 dB in a previous study within Cochlear comparing outcomes with a BP100 sound processor on a Softband versus on an abutment.

1.4.3 Overall sample size considerations

In order to achieve 90% power both for the primary analysis (PTA4, Baha Attract vs. unaided) and the secondary analysis of the primary variable (PTA4, Baha Attract vs. Softband), 46 evaluable subjects are needed. To compensate for a 10% drop out rate in the study 52 subjects will be included in the investigation.

2 STUDY POPULATIONS

2.1 Definition of Study Populations

The final definition of the analysis sets (ITT, PP and Safety) will be taken at the clean file meeting before database lock.

2.1.1 Intent-to-Treat Population (Full Analysis Set)

The Intention-to-Treat population (ITT) will include all subjects who have received the surgical intervention.

2.1.2 Per-Protocol Population

The Per Protocol population (PP) will include subjects that have completed the investigation according to the protocol. Subjects that were incorrectly included or were considered major protocol violators should be removed from the PP population.

2.1.3 Safety Population

The Safety population consists of all surgically treated subjects

3 STUDY VARIABLES

3.1 Baseline and pre operation variables

3.1.1 Demographics and Baseline Characteristics

- Age (years), calculated from date of birth and date of
- Gender
  - Male
  - female
- Ethnicity
  - American Indian/Alaska Native,
  - Asian,
  - Black or African American,
  - Native Hawaiian/Pacific Islander,
  - White,
  - Other
- Weight (kg), (convert lbs to kg)
- Height (cm), (convert in to cm)
- Nicotine use
  - Subject does not smoke
  - <= 10cig/day
  - 11-20 cig/day
  - 21-40 cig/day
  - > 40 cig/day
- Site
  - Nijmegen, Netherlands
  - Manchester, UK
  - Birmingham, UK
  - Milwaukee, USA
  - Kajetany, PL
- Country
  - Netherlands
  - UK
  - USA
  - Poland

3.1.2 Pre operation variables

- Treatment ear

  - Right
  - Left
- Type of hearing loss
  - Conductive/mixed
  - SSD
- Aetiology
  - (Chronic) Infection
  - Tumour
  - Trauma
  - Malformation
  - Otosclerosis
  - Other
- Current hearing aid
  - Yes
  - No
- Selection of sound processor
  - Baha BP110
  - Baha 4
  - Baha 5

3.1.3 Audiogram

Audiogram at Visit 1, Air condition/Bone conduction, Right/Left (transferred to Baha side/Non Baha side), Unmasked/Masked for 250, 500, 750, 1000, 1500, 2000, 3000, 4000, 6000 and 8000 Hz.

3.1.4 Medical and Surgical History

- Medical history will be coded using MedDRA 18.0.
- Surgical history will be coded using MedDRA 18.0.

3.1.5 Prior and Concomitant Medications

Prior medication is medication that has been used between Visit 1 and Surgery. Concomitant medications is medications used after surgery to end of study. Medications are coded according to WHO CC ATC.

3.1.6 Concomitant Treatments/Procedures

Concomitant Treatments/Procedures between Visit 1 and end of study will be collected. These terms will not be coded.

3.2 Efficacy Variables

3.2.1 Primary Efficacy Variable

Threshold audiometry: PTA4 (mean of 500, 1000, 2000 and 4000Hz)

3.2.2 Secondary Efficacy Variables

- Thresholds audiometry: 250, 500, 1000, 2000, 3000, 4000, and 6000 Hz at visit 1, w 4, m 6, m 12 and m 24.
- Adaptive speech recognition in noise (50% performance) at visit 1, w 4, m 6, m 12 and m 24.

- Speech perception in quiet (50dB, 65dB and 80dB SPL) at visit 1, w 4, m 6, m 12 and m 24.
- BC Direct thresholds at visit 1 and w 4
- Generic quality of life scale: Health Utility Index (HUI):
    - Health related quality of life score for overall health
    - Vision score
    - Hearing score
    - Speech score
    - Ambulation/mobility score
    - Dexterity score
    - Self-care score
    - Emotion score
    - Cognition score
- Abbreviated Profile of Hearing Aid Benefit (APHAB):
    - Ease of Communication
    - Reverberation
    - Background Noise
    - Aversiveness
    - Global score
- The Speech, Spatial and Qualities of Hearing Scale (SSQ)

Surgical variables

- Soft tissue thickness (mm)
- Surgery time (time of first incision to time of last suture), (min)
- Soft tissue thinning performed
    - Yes
    - No
- Bone polishing/removal performed
    - Yes
    - No
- ISQ Low
- ISQ High
- BI300 length
    - 3 mm
    - 4 mm

Questions regarding Sound processor magnet by visit and changes over time (w 4, w 6, w 12, m 6, m 12 and m24)

- Choice of SP Magnet (SPM1 (weakest), SPM2, SPM3, SPM4, SPM5, SPM6 (strongest))
- Mean Magnetic retention force (mean of three values). If there is large variations within the three measurements median of the three values will be used instead.

Questions about usage will be collected for w 6, w 12, m 6, m 12 and m24:

- Daily use of SP (hours/day)
- Number of times SP fell off during last week
- Number of times SP fell off during last week per Daily use (times/hours/day)
- Number of Soft pad changes per week (calculated from changes last week and changes last month)
- Number of Soft pad changes per Daily use (changes/hours/day)

3.3 Safety Variables

3.3.1 Adverse Events

Treatment emergent adverse events will be presented. Treatment emergent is defined as an event happening at or after surgery. Three predefined AE categories (Magnetic retention difficulties, Pressure related skin complications, Pain/Discomfort) will be used, and if other is checked those will be MedDRA (version 18.0) coded.

- Adverse Event (AE) is all reported events
- Adverse Device Effect (ADE) is events that is Related to the device (Probably) or Related to the procedure (Probably)
- Serious Adverse Event (SAE) is events that has been marked as Serious
- Serious Adverse Device Effect (SADE) is events that has been marked as Serious and also marked as Related to the device (Probably) or Related to the procedure (Probably)

3.3.2 Pain and numbness

- Pain/discomfort (w 6, w 12, m 6, m 12 and m 24)
  - No discomfort and/or pain.
  - Slight discomfort and/or pain
  - Discomfort and/or pain
  - Excessive discomfort and/or pain

- Numbness (pin) (d 10, w 4, w 6, w 12, m 6, m 12 and m 24)
  - No numbness
  - Numbness within 2 cm from the implant
  - Numbness within and beyond 2 cm from the implant
- Numbness (cotton swab) (d 10, w 4, w 6, w 12, m 6, m 12 and m 24)
  - No numbness
  - Numbness within 2 cm from the implant
  - Numbness within and beyond 2 cm from the implant

3.3.3 Device deficiency and Soft tissue status

Device deficiency will be collected at d 0, d 10, w 4, w 6, w 12, m 6, m 12 and m 24.

- Has any device deficiency occurred?
  - Yes
  - No

Soft tissue status will be collected at d 10, w 4, w 6, w 12, m 6, m 12 and m 24.

- Any signs of infection, inflammation, skin necrosis and/or scar hypertrophy?
  - Yes
  - No

3.3.4 Implant loss/removal and Implant magnet loss/removal

- Has the patient lost/removed the implant?
  - Yes
  - No
- Date of loss/removal of implant
- Has the patient lost/removed the implant magnet?
  - Yes
  - No
- Date of first loss/removal of implant magnet

4 STATISTICAL METHODOLOGY

4.1 General Methodology

Since all included subjects will have measurements of the primary and important secondary efficacy variables for unaided hearing, with the sound processor on a Softband and with the Baha Attract System, all statistical analyses will be paired. All statistical analyses will be non-parametric. In order to choose the most powerful test, the Fisher's non-parametric permutation test for paired observations will be used for all paired analyses of continuous variables. The permutation tests use the measured values and not only the ranks in the calculations. For paired analysis of dichotomous and ordered categorical variables the Sign test will be used.

The analyses will be performed in the following priority:

1. Baha Attract System vs. Unaided
2. Baha Attract System vs. the sound processor on a Baha Softband

In addition to the change variables the distribution of all efficacy variables will be presented by visit, where applicable.

The main efficacy analysis will be performed on the ITT population and complementary efficacy analyses will be performed on the PP population. The main analysis will be performed after the 6 month visit. A complementary analysis will be performed 18 months after the main analysis (24-month visit). All significance tests will be two-sided and performed at the 5% significance level.

Imputation of missing values will be performed for all efficacy variables. No imputation of baseline values will be made. Imputations will be made according to the following rules:

1. If a value is missing at the end of a patient last observation will be carried forward
2. If a missing value is occurring between two time points with values, an interpolation will be made for continuous variables and for categorical variables the value from the previous visit will be carried forward.

The distribution of continuous variables as well as change in continuous variables will be given as n, mean, SD, SEM, Median, Min and Max and the distribution of dichotomous and categorical variables will be given as number and percentages.

Adverse Events, Device deficiencies, Surgical variables, Demographics Baseline, Questions, Magnetic force and Magnet strength variables will only be analysed descriptively.

4.2 Patient Disposition and Data Sets Analyzed

The number of subjects included in each of the ITT, PP and Safety populations will be summarized. Subjects who completed the study and subjects who withdrew from study prematurely will also be presented with a breakdown of the reasons for withdrawal by treatment group for the ITT, PP and safety populations.

Reasons:

- Eligibility failed
- Intra-operative failure

- Subject non-compliance
- Major Protocol Deviation affecting the primary endpoint
- Lost to Follow-up
- Discretion of the investigator
- Subject withdrew Consent
- Intolerable Adverse Event
- Death
- Other

4.3 Protocol Deviations

Major protocol deviations are those that are considered to have an effect on the analysis. The number of patients with major protocol deviations will be summarized per treatment group. A list of protocol deviations will be produced.

4.4 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be descriptively summarized for the ITT and PP populations.

4.5 Pre operation variables

Pre operation variables will be summarized for the ITT and PP populations and analyzed according to the methods described in section “General Methodology” above.

4.6 Audiogram

Audiogram at visit 1 will be presented for the ITT and PP populations by Air condition/Bone conduction, Baha side/Non Baha side, Unmasked/Masked for 250, 500, 750, 1000, 1500, 2000, 3000, 4000, 6000 and 8000 Hz by SSD and Conductive/Mixed patients. In addition to the tables, figures will be produced for the audiogram data.

4.7 Medical and Surgical History

Medical and surgical history, one at a time, will be summarized by system organ class (SOC) and preferred term (PT) for each treatment group for ITT population.

4.8 Prior and Concomitant Medications

Prior and concomitant medication will be summarized by higher level anatomical therapeutic classification (ATC) group and generic term for each treatment group for ITT population.

4.9 Concomitant Treatments/Procedures

Concomitant treatments/procedures will be listed for the ITT population. A special mark-up will be done whether to tell if the treatment was performed before or/after surgery

4.10 Efficacy Analyses

4.10.1 Primary Efficacy Analysis

Primary efficacy analysis will be determined by analysis of change in free-field threshold audiometry:
PTA4 (mean of 500, 1000, 2000 and 4000Hz), from unaided versus Baha Attract System at the 6 months visit for the ITT population, using Fisher's two-sided non-parametric permutation test for paired observations at a significance level of 0.05.

4.10.2 Secondary Efficacy Analyses

Comparison regarding change from unaided hearing to Baha Attract System will be done according to the general methodology with Fisher's non-parametric permutation test for paired observations for the following variables:

- Threshold audiometry: PTA4 (Mean of 500, 1000, 2000 and 4000 Hz) at 4 weeks, 12 and 24 months
- Threshold audiometry: 250, 500, 1000, 2000, 3000, 4000 and 6000 Hz at 4 weeks, 6, 12 and 24 months
- Adaptive speech recognition in noise (50% performance) at 4 weeks, 6, 12 and 24 months
- Speech in quiet (50dB, 65dB and 80dB) at 4 weeks, 6, 12 and 24 months
- HUI3 at 6 and 24 months
- APHAB at 6 and 24 months
- SSQ at 6 and 24 months

Comparison of the Baha Attract System with the same sound processor worn on a Softband will be done according to the general methodology with Fisher's non-parametric permutation test for paired observations for the following variables:

- Threshold audiometry: PTA4 (Mean of 500, 1000, 2000 and 4000 Hz) at 4 weeks, 6, 12 and 24 months
- Threshold Audiometry: 250, 500, 1000, 2000, 3000, 4000 and 6000 Hz at 4 weeks, 6, 12 and 24 months
- Adaptive speech recognition in noise (50% performance) at 4 weeks, 6, 12 and 24 months
- Speech in quiet (50dB, 65dB and 80dB SPL) at 4 weeks, 6, 12 and 24 months

Magnetic force studied both total and by SP magnet. Changes in SP magnet strength will also be presented graphically in a flow graph.

All secondary efficacy analyses will be performed for both the ITT population and PP population. PTA4 will also be analyzed for the PP population in the same fashion as in the primary analysis.

Analyses of Threshold Audiometry, Adaptive speech recognition in noise and Speech in quiet, BC Direct, HUI, APHAB and The Speech, SSQ will be a made totally and also by SSD and Conductive/Mixed patients. This will be made only for the ITT populations.

4.11 Safety Analyses

4.11.1 Adverse Events

Only treatment-emergent AEs will be included in the summaries for safety population.

A summary of subjects reporting at least one of the following AEs will be presented in an overview table:

- Any AE
- Any SAE
- Any Adverse Device Effect (ADE)
- Any Serious Adverse Device Effect (SADE)

Summaries per predefined AE, SOC and PT presenting n (%) of AEs and n (%) of subjects with at least one AE will be provided for:

- All AE
- All SAE
- All Adverse Device Effect (ADE)
- All Serious Adverse Device Effect (SADE)

4.11.2 Pain/discomfort, Numbness, Device deficiency and Soft tissue status

Pain/discomfort, Numbness, Device deficiency and Soft tissue status will be presented by visit.

4.11.3 Implant loss and magnet loss

Analysis of Implant loss/removal, magnet implant loss/removal and Implant or Implant magnet loss/removal will be performed. Analyses of loss and removal will also be analysed separately. Data will be presented in tables and KM-figures.

5 INTERIM ANALYSES

No interim analysis is planned. The main analysis is made at 6 month and another follow-up analysis at 24 months (18 months after the 6 months analysis).

6 CHANGES OF ANALYSIS FROM PROTOCOL

No changes of the analyses according to the protocol are made.

7 LISTING OF TABLE, FIGURES AND LISTINGS

7.1 Listing of Tables

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7.2 Listing of Figures

7.3 Listing of Listings

Listings are decided outside of this SAP.

8 REFERENCES

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