Statistical Analysis Plan

ATB System

CBAS5539

Clinical performance of a new implant system for bone conduction hearing

Open, prospective, multicentre clinical investigation. 3-month investigation with an additional 9 months of follow-up

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADE	Adverse Device Effect
AE	Adverse Event
AESI	Adverse events of special interest
APHAB	Abbreviated Profile of Hearing Aid Benefit
ATB	Active transcutaneous Baha
ATC	Anatomic Therapeutic Chemical classification system
BC	Bone Conduction
BFS	Baha Fitting Software
d	Day
dB	Decibel
CTCAE	Common Terminology Criteria for Adverse Events
DD	Device Deficiency
HUI	Health Utilities Index
Hz	Hertz
ITT	Intention to treat
m	Month
Max	Maximum
min	Minute
Min	Minimum
mm	Millimetre
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
w	Week
WHO CC	World Health Organization Collaborating Centre for Drug Statistics Methodology

1 STUDY DETAILS

1.1 Study Objectives

Objectives and outcome measures	
Primary objective	**Outcome measures/endpoints**
To compare hearing performance with the Investigational device and the unaided hearing situation	• Thresholds audiometry, free-field [PTA4, Mean of 0.5, 1, 2 and 4 kHz]. Investigational device (at 3 months) vs. Unaided. • Adaptive speech in noise Matrix Test [speech-to-noise ratio, 50% speech understanding] (at 3 months). Investigational device vs. Unaided.

Secondary objectives	Outcome measures/endpoints
To compare hearing performance with the Investigational device and the unaided hearing situation	• Thresholds audiometry, free-field [PTA4, Mean of 0.5, 1, 2 and 4 kHz]. Investigational device (4 weeks, 6 and 12 months) vs. Unaided. • Thresholds audiometry, free-field [0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0 and 8.0 kHz]. Investigational device vs. Unaided. • Adaptive speech in noise Matrix Test [speech-to-noise ratio, 50% speech understanding]. Investigational device (6 and 12 months) vs. Unaided. • Speech in quiet [% correctly perceived words at 50dB, 65dB and 80dB SPL]. Investigational device vs. Unaided. • Feedback measurements. Investigational device.
To compare the self-reported assessments of hearing outcome with the Investigational device and in a preoperative hearing situation	• Abbreviated Profile of Hearing Aid Benefit (APHAB). Investigational device vs. Unaided. • Health Utilities Index (HUI23S1EN.15Q). Investigational device vs. preoperative hearing situation • Speech, Spatial and Qualities of Hearing Scale (SSQ). Investigational device vs. Unaided.
To collect surgical information	• Soft tissue thickness • Soft tissue reduction performed • Type of anaesthesia

	• Surgery time • Bone polishing/removal at the actuator site • BI300 Implant length • Location of BI300 Implant • Surgical incision type/location
To collect information about the magnet choice and daily use of sound processor	• Daily usage time • Comfort • Softpad use • Choice of magnet strength
To measure hearing performance preoperatively with a Baha BP110 Power Sound Processor on a Baha Softband	• Thresholds audiometry, free-field [PTA4, Mean of 0.5, 1, 2 and 4 kHz]. • Thresholds audiometry, free-field [0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0 and 8.0 kHz]. • Speech in quiet [% correctly perceived words at 50dB, 65dB and 80dB SPL] • Adaptive speech in noise [speech-to-noise ratio, 50% speech understanding]. • BC Direct [0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0 and 6.0 kHz].

Tertiary objective	**Outcome measures/endpoints**
To measure hearing performance preoperatively with a current hearing aid (if used by the patient)	• Adaptive speech in noise [speech-to-noise ratio, 50% speech understanding].

Safety objectives	**Outcome measures/endpoints**
The primary safety analysis will be performed at 6 months	
Implant site evaluations	Numbness
Adverse Events and concomitant medication/treatment	Information will be collected from visit 2 and onwards.
Device deficiency	Information will be collected from Visit 2 and onwards.
Audiogram	Bone conduction thresholds preoperative and postoperative

1.2 Study Design

Open, prospective, multicentre clinical investigation. 3-month investigation (primary efficacy analysis) with an additional 9 months of follow-up. Primary safety analysis occurs during the investigation at 6 months.

1.3 Flowchart

	Visit 1 Pre-op testing	**Visit 2** Surgery	**Visit 3** Suture removal	**Visit 4** Fitting	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**
Visit time point		**0**	**2W**	**4W**	**6W**	**3M**	**6M**	**12M**
Visit window			± 5D	± 1W	± 1W	± 2W	± 3W	± 4W
Demographics	X							
Medical history	X							
Baseline characteristics	X							
Audiogram	X					X[6]		X[6]
Eligibility criteria	X							
Informed consent	X							
Soft tissue thickness	X or X							
Surgery[1]		X						
IOTS		X						
Suture removal			X					
Sound processor fitting	X[2]			X	X	X	X	X
Magnet choice				X	X	X	X	X
BC Direct	X[2]			X	X	X	X	X
Feedback measurements				X	X	X	X	X
Free field thresholds	X[2,3.4]			X		X	X	X
Speech recognition in quiet	X[2,3, 4]			X		X	X	X
Speech recognition in noise	X[2,3, 4]			X		X	X	X
APHAB	X[3]					X		X
HUI	X[4]					X		X
SSQ	X[3]					X		X
Daily use[5]					X	X	X	X
Numbness			X	X	X	X	X	X
Device deficiency		X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X
Concomitant medication/treatment		X	X	X	X	X	X	X
Extra visits as needed								

	Visit 1 Pre-op testing	Visit 2 Surgery	Visit 3 Suture removal	Visit 4 Fitting	Visit 5	Visit 6	Visit 7	Visit 8
Visit time point		**0**	**2W**	**4W**	**6W**	**3M**	**6M**	**12M**

[1] *Surgical variables: Soft tissue thickness (mm), Surgery time (time between first incision and last suture), Bone polishing/removal at the actuator site, BI300 Implant length (4mm, 3 mm), Location of BI300 Implant (mm), Type of anaesthesia (general, local), Soft tissue reduction performed (yes, no), Surgical incision type.*

[2] *BahaPower Sound Processor (BP110) on Baha Softband*

[3] *Unaided*

[4] *In a preoperative hearing situation*

[5] *Daily use: Usage time (hours/day), Comfort (visual analogue scale), Softpad use*

[6] *Only bone conduction*

1.4 Device/Treatment Groups

Only one device group is included in this study.

1.5 Sample Size

1.5.1 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 or 10 SNR between the unaided situation and the ATB System at the 3 months visit with Fisher's non-parametric permutation test for paired observations, one-sided test with significance level 0.025, on the ITT population 11 (PTA-4) and 13 (SNR) evaluable subjects are needed. The sample size was calculated using simulation on study id CBAS5675 (Cochlear 2017) data which used the simulated ATB system on Mixed/Conductive subjects. The within subject SD for change Unaided to ATB in PTA4 was 9.5 dB and 11.3 SNR. Since significant result want to be detected in both arms (SSD and Conductive/Mixed) 13+13=26 subjects should be included in the investigation.

1.5.2 Sample size estimation for the primary safety analysis at 6 months

Primary safety analysis will be evaluated at 6 months and an estimation of 50 subjects results in 25 patient years at 6 months which will yield enough safety data for the primary safety analysis. At the 12 months analysis 50 subjects results in 50 patient years.

1.5.3 Overall sample size considerations

In order to achieve 90% power both for the primary analysis (PTA4 and SNR, Investigational Device vs. unaided) and the primary safety analysis, 50 evaluable subjects are needed. Each arm SSD and Conductive/Mixed should at least consist of 13 patients to assure a power of 90% in both arms for the primary analyses.

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 undergone 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 variables

3.1.1 Demographics

- Age (years), calculated from date of birth and date of
- Gender
- Ethnicity
- Nicotine use
- Site
- Country

3.1.2 Baseline Characteristics

- Treatment ear
  - Right
  - Left
- Type of hearing loss
  - Conductive/mixed
  - SSD
- Aetiology
  - (Chronic) Infection
  - Tumour
  - Trauma
  - Malformation
  - Otosclerosis
  - Other
- Current hearing aid
  - Yes
  - No

3.1.3 Medical and Surgical History

- Medical history will be coded using CTCAE.
- Surgical history will be coded using CTCAE.

3.1.4 Prior and Concomitant Medications

Prior medication is defined as medication used up surgery. Concomitant medications are medications used from Surgery to end of study. Medications are coded according to WHO CC ATC.

3.1.5 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/endpoints

3.2.1 Primary Efficacy Variables/endpoints

- Threshold audiometry: PTA4 (mean of 500, 1000, 2000 and 4000Hz) at visit 1 (unaided) vs 3 months post-surgery (aided).
- Change in Adaptive speech recognition in noise (50% performance) from unaided versus Investigational device at the 3 months visit.

3.2.2 Secondary Efficacy Variables/endpoints

- Abbreviated Profile of Hearing Aid Benefit (APHAB) at visit 1 (unaided), m 3, m 6 and m 12:
  - Global score
  - Ease of Communication
  - Reverberation
  - Background Noise
  - Aversiveness
- Thresholds audiometry: PTA-4, 250, 500, 1000, 2000, 3000, 4000, and 6000 Hz at visit 1, w 4, m 3, m 6 and m 12
- Speech perception in quiet (50dB, 65dB and 80dB SPL) at visit 1, w 4, m 3, m 6 and m 12
- Adaptive speech recognition in noise (50% performance) at visit 1, w 4, m 3, m 6 and m 12
- Feedback measurement at each frequency at visit w 4, w 6, m 3, m 6 and m 12

- Generic quality of life scale: Health Utility Index (HUI) at visit 1 (unaided), m 3, m 6 and m 12:
  - 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
- The Speech, Spatial and Qualities of Hearing Scale (SSQ) at visit 1 (unaided), m 3, m 6 and m 12

Surgical variables

- Soft tissue thickness (mm)
- Surgery time (time of first incision to time of last suture), (min)

- Type of anaethesia
- Soft tissue thinning performed
  - Yes
  - No
- Bone polishing/removal below the actuator site performed
- BI300 length
  - 3 mm
  - 4 mm
- Location of BI300 Implant
- Surgical incision/location

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

- Daily use of sound processor (hours/day)
- Softpad use
- Question about comfort with the SP, using VAS, will be collected at w 4, w 6, m 3, m 6 and m 12.
- Magnet choice will be recorded at w 4, w 6, w 12, m 6 and m 12.

BC Direct thresholds at visit 1, w 4, w 6, m 3, m 6 and m 12

3.3 Safety Variables/Endpoints

3.3.1 Implant site evaluation

Evaluation about numbness around the implant site will be performed at w 2, w4, w 6, m 3, m 6 and m 12.

- Total sensibility %
- Gnostic sensibility % (cotton swab) at 30 mm and 60 mm for Cranial, Caudal, Anterior and Posterior
- Vital sensibility % (sharp wodden) at 30 mm and 60 mm for Cranial, Caudal, Anterior and Posterior

3.3.2 Adverse Events

Adverse events from visit 2 and onward will be presented.

- 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)
- The following AEs are defined as adverse events of special interest (AESIs):
  - AE that interfere with the daily use of the medical device(s)
  - AE at the site of the implant that lead to
    - Revision surgery including explantation
    - Severe soft tissue complication
    - Prescription of antibiotics

3.3.3 Device deficiency

Device deficiency will be collected at d 0, w 2, w 4, w 6, m 3, m 6 and m 12.

- Has any device deficiency occurred?
  - Yes

- No

3.3.4 Audiogram

Audiogram at Visit 1, Air condition/Bone conduction, Right/Left (transferred to test side/Non test side), Unmasked/Masked for 250, 500, 750, 1000, 1500, 2000, 3000, 4000, 6000 and 8000 Hz. At 3 months visit and 12 months visit test side audiogram, bone conduction (unmasked and if needed masked) thresholds at 250, 500, 750, 1000, 1500, 2000, 3000, 4000 and 6000Hz will be collected.

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 Investigational device and with a Baha power sound processor on a Baha Softband, 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. Investigational Device vs. Unaided
2. Investigational Device vs. Baha power 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 3 month visit. A complementary analysis will be performed 9 months after the main analysis (12-month visit). All significance tests will be one-sided and performed at the 2.5% significance level to demonstrate an improvement with Investigational Device.

The hierarchical testing procedure below is introduced to guarantee that the probability of Type I error is < 2.5% for all confirmative statements. The order of the hierarchical testing procedure will be:

1. PTA 4 pre-operative unaided vs 3 months (Primary efficacy analysis)
2. Adaptive speech recognition in noise (50% performance), speech to noise ratio (SNR) pre-operative unaided vs 3 months
3. Speech in quiet at 65dB SPL pre-operative unaided vs 3 months
4. APHAB Global pre-operative unaided vs 3 months aided
5. Hearing attribute (HUI-III) pre-operative unaided vs 3 months
6. Mean of the 12 items in the SSQ pre-op unaided vs 3 months

If the first analysis is significant the probability mass 0.025 will go to the second analysis. If the second analysis is also significant the probability mass 0.025 will go to the third analysis and so on. When the first non-significant analysis is reached this and all analyses thereafter will be non-confirmative while the previous analyses will be confirmative. If the first analysis is non-significant no analysis will be confirmative.

The hierarchical testing will be made for each arm separately (SSD and Mixed/Conductive) and not totally.

We plan to analyse the similarity of the primary efficacy results among sites using non-parametric one way analyses of variance (Kruskal-Wallis test) of the difference between Unaided and ATB at 3 months. This will only be made totally and not by SSD and Mixed conductive.

Imputation of missing values will be performed for all efficacy variables. No imputation of baseline values or baseline carry forward 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. One sided 97.5% CI will be presented where applicable.

Numbness, Adverse Events, Device deficiencies, Comfort, Usage, Surgical variables, Demographics, Baseline, Questions, Magnet strength variables will only be analysed descriptively.

4.2 Timing of analyses

The main efficacy analysis is made at 3 months and another follow-up analysis at 12 months. The primary Safety analysis will be made at 6 months.

- When locking the data at 3 months both efficacy and safety will be evaluated.
- When locking the data at 6 months only safety will be evaluated.
- When locking the data at 12 months both efficacy and safety will be evaluated.

4.3 Patient Disposition and Data Sets Analysed

The number of subjects included in each of the ITT, PP and Safety populations will be summarised. 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.

4.4 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 summarised per treatment group. A list of protocol deviations will be produced.

4.5 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be descriptively summarised by SSD and Mixed/Conductive and totally for the ITT and PP populations.

4.6 Pre operation variables

Pre operation variables will be summarised by SSD and Mixed/Conductive and totally for the ITT and PP populations and analysed according to the methods described in section “General Methodology” above.

4.7 Medical and Surgical History

Medical and surgical history, one at a time, will be summarised by CTCAE term by SSD and Mixed/Conductive and totally for ITT population.

4.8 Prior and Concomitant Medications

Prior and concomitant medication will be summarised by higher level anatomical therapeutic classification (ATC) group and generic term by SSD and Mixed/Conductive and totally 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) and change in Adaptive speech recognition in noise (50% performance), from unaided versus Investigational device at the 3 months visit for the ITT population, using Fisher’s one-sided non-parametric permutation test for paired observations at a significance level of 0.025 to demonstrate an improvement in PTA4. Each arm SSD and Conductive/Mixed will be tested separately. Both PTA4 and SIQ must be significant at alpha 0.025 for the primary analysis to be considered as confirmative in each arm separately. In addition, a pooled analysis for all subjects will be made.

Group mean free-field PTA4 (average of 500, 1000, 2000, and 4000 Hz) with the Osia System at the 3-month postoperative interval will be improved over that measured preoperatively in the unaided condition (baseline).

This endpoint is represented by the following hypotheses:

$$\mathrm{H}_0\colon \mu_F - \alpha_0 \geq 0,$$

$$\mathrm{H}_\mathrm{a}\colon \mu_F - \alpha_0 < 0,$$

where:

α_0 = baseline preoperative PTA4;

μ_F = mean follow-up PTA4 3 months postoperative.

Group mean Adaptive speech recognition in noise (50% performance), speech to noise ratio (SNR) with the Osia System at the 3-month postoperative interval will be improved over that measured preoperatively in the unaided condition.

This endpoint is represented by the following hypotheses:

$H_0: \mu_F - \alpha_0 \geq 0,$

$H_a: \mu_F - \alpha_0 < 0,$

where:

α_0 = baseline preoperative Adaptive speech recognition in noise (50% performance), speech to noise ratio (SNR);

μ_F = mean follow-up Adaptive speech recognition in noise (50% performance), speech to noise ratio (SNR) 3 months postoperative.

A sensitivity analysis of the primary variable will be done for complete cases.

The primary analyses will be performed regardless of what Osia Fitting Software version (1.0.2 OFS or 1.0.3 OFS) used at 3 months (see chapter 4.12).

4.10.2 Secondary Efficacy Analyses

The secondary efficacy objectives in the hierarchical testing will be tested using the following hypothesis:

Group mean Speech in quiet at 65dB with the Osia System at the 3-month postoperative interval will be improved over that measured preoperatively in the unaided condition.

This endpoint is represented by the following hypotheses:

$H_0: \mu_F - \alpha_0 \leq 0,$

$H_a: \mu_F - \alpha_0 > 0,$

where:

α_0 = baseline preoperative word recognition score;

μ_F= mean follow-up word recognition score 3 months postoperative.

Group mean APHAB Global score with the Osia System at the 3-month postoperative interval will be improved over that measured preoperatively in the unaided condition.

This endpoint is represented by the following hypotheses:

$H_0: \mu_F - \alpha_0 \geq 0,$

$H_a: \mu_F - \alpha_0 < 0,$

where:

α_0 = baseline preoperative APHAB Global score;

μ_F= mean follow-up APHAB Global score 3 months postoperative.

Group mean Hearing attribute (HUI-III) with the Osia System at the 3-month postoperative interval will be improved over the preoperative hearing situation.

This endpoint is represented by the following hypotheses:

H_0: $\mu_F - \alpha_0 \leq 0$,

H_a: $\mu_F - \alpha_0 > 0$,

where:

α_0 = baseline preoperative Hearing attribute (HUI-III);

μ_F= mean follow-up Hearing attribute (HUI-III) 3 months postoperative.

Group mean of the 12 items in the SSQ with the Osia System at the 3-month postoperative interval will be improved over the preoperative hearing situation.

This endpoint is represented by the following hypotheses:

H_0: $\mu_F - \alpha_0 \leq 0$,

H_a: $\mu_F - \alpha_0 > 0$,

where:

α_0 = baseline preoperative mean of the 12 items in the SSQ;

μ_F= mean follow-up mean of the 12 items in the SSQ 3 months postoperative.

Comparison regarding change from unaided hearing (if applicable) to Investigational device will be done according to the general methodology with Fisher's non-parametric permutation test for paired observations for the following variables:

- APHAB at 3, 6 and 12 months
- Threshold audiometry: PTA4 (Mean of 500, 1000, 2000 and 4000 Hz) at 4 weeks, 6 and 12 months
- Threshold audiometry: 250, 500, 1000, 2000, 3000, 4000 and 6000 Hz at 4 weeks, 3, 6, and 12 months
- Adaptive speech recognition in noise (50% performance) at 4 weeks, 3, 6 and 12 months
- Speech in quiet (50dB, 65dB and 80dB) at 4 weeks, 3, 6 and 12 months
- Feedback measurement at each frequency at 4 and 6 weeks, 3, 6 and 12 months
- HUI-III at 3, 6 and 12 months
- SSQ at 3, 6 and 12 months

Comparison of the Investigational device with a Baha Power sound processor worn on a Baha 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, 3, 6 and 12 months
- Threshold audiometry: 250, 500, 1000, 2000, 3000, 4000 and 6000 Hz at 4 weeks, 3, 6, and 12 months

- Adaptive speech recognition in noise (50% performance) at 4 weeks, 3, 6 and 12 months
- Speech in quiet (50dB, 65dB and 80dB) at 4 weeks, 3, 6 and 12 months
- BC Direct at 4 and 6 weeks, 3, 6 and 12 months.

Choice of SP magnet and change of 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 analysed 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 SSQ will be made totally and also by SSD and Conductive/Mixed patients. This will be made only for the ITT population.

4.10.3 Tertiary Efficacy Analyses

As tertiary efficacy analysis adaptive speech in noise [speech-to-noise ratio, 50% speech understanding] with a current hearing aid (if used by the patient) will be presented. Summarization will be made for the ITT population totally and by SSD and Mixed/Conductive (if sufficient data is collected).

4.11 Safety Analyses

The primary safety analysis will be evaluated at 6 months.

4.11.1 Implant site evaluation

Evaluation about numbness will be presented by visit. Changes from first measurement may be evaluated.

4.11.2 Adverse Events

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)
- Any AESI

Summaries by CTCAE term 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)
- All AESI

4.11.3 Device deficiency

Device deficiency will be presented by visit.

4.11.4 Audiogram

Audiogram (Air and Bone conduction), test side for 250, 500, 750, 1000, 1500, 2000, 3000, 4000, 6000 and 8000 Hz by SSD and Conductive/Mixed patients will be presented at visit 1, 6 and 8. At visit 6 and 8 is only bone conduction performed.

4.12 Handling of change in Osia version of Fitting Software

Due to the change in version of Osia Fitting Software (OFS) during the study (from 1.0.2 to 1.0.3) analyses are planned for taking care of this. All patients that are already fitted with OFS version 1.0.2 will switch from 1.0.2 OFS to the new 1.0.3 OFS at a certain visit (1 year at the latest) and some will use the new 1.0.3 OFS from start. This means that some patients will, at a certain time point, have done their measurements based on different OFS. We do not intend to change the primary efficacy analyses due to the change in OFS.

When both 1.0.2 OFS and 1.0.3 OFS are measured (at a certain visit when the change is implemented) the new 1.0.3 OFS version will be used in the planned analyses.
The following analyses are planned due the change of OFS:

1. Frequency of “OFS change visit” in order to present the distribution of when the change took place. If a patient used the 1.0.3 from the beginning Visit 4 Fitting will be presented.
2. Descriptives and changes from unaided for free-field thresholds, speech in quiet test and speech in noise test by visit will be presented by 1.0.2 OFS and 1.0.3 OFS without statistically testing.
3. For the patients who initially used 1.0.2 OFS the free-field thresholds, the speech in quiet test and the speech in noise test will be compared at the visit when the change took place. Results will be summarized for 1.0.2 OFS, 1.0.3 OFS and for the difference between the versions. This will be made totally but also by visit (when the change took place). Scatter plots of 1.0.2 OFS (x) vs 1.0.3 OFS (y) with visit where the change took place as group (colour/symbol) indicator will be produced. In addition, line plots of measure (y) vs OFS version (y), one line per patient with visit where the change took place as group (colour/symbol) indicator will be produced.

5 INTERIM ANALYSES

An interim safety analysis will be performed when all subjects at the site in Melbourne have completed the 3 month visit (i.e. visit 6). Based on the result of this interim analysis a ‘go/no go’ decision will be taken if to proceed with the investigation at the other sites. Focus of this safety analysis will be on reported Serious Adverse Event (SAEs) and Adverse Event of Special Interest (AESIs), i.e.:

- AE that interfere with the daily use of the medical device(s)
- AE at the site of the implant that lead to
  - Revision surgery including explantation
  - Severe soft tissue complication
  - Prescription of antibiotics

The 'go/no go' decision will be taken by the co-ordinating investigator and the Sponsor in collaboration with the principal investigator at the Melbourne site

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

Table 14.1.1	Patient Disposition and Data Sets Analysed
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Table 14.1.3.1	Demographics and Baseline Characteristics (ITT Population)
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7.2 Listing of Figures

To be decided later.

7.3 Listing of Listings

Listings are decided outside of this SAP.

8 REFERENCES

9 APPENDIX