

STATISTISKA KONSULTGRUPPEN		Statistical Analysis Plan	
Protocol: Clinical and health economic evaluation with a new Baha abutment design combined with a minimally invasive surgical technique		Protocol No: CBAS5439	
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Statistical Analysis Plan

FINAL

CBAS5439

Clinical and health economic evaluation with a new Baha abutment design combined with a minimally invasive surgical technique

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Author

Name/Title: Mattias Molin / Statistician, Statistiska konsultgruppen	
Signature:	Date

Approvals

Name/Title: Stina Wigren, Clinical Research Manager, Cochlear	
Signature:	Date
Name/Title: Professor Robert Stokroos, Co-ordinating investigator, University Hospital Maastricht	
Signature:	Date

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Revisions

Version	Description of Changes	Date

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADE	Adverse device event
AE	Adverse event
APHAB	Abbreviated profile of hearing aid benefit
ATC	Anatomic Therapeutic Chemical classification system
AUC	Area under the curve
CI	Confidence interval
CRF	Case report form
HRQL	Hearing related quality of life
HUI	Health utilities index
ISQ	Implant stability quotient
ITT	Intent to treat
LOCF	Last observation carry forward
MedDRA	Medical Dictionary for Regulatory Activities
POSAS	The patient and observer scar assessment scale
PP	Per protocol
PT	Preferred term
QALY	Quality-adjusted life year
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
SSD	Single sided deafness

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1 SCOPE

This SAP intends to answer the questions raised in the protocol. This SAP does not include the Health Economic evaluation at 3 years.

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2 STUDY DETAILS

2.1 Study Objectives

This randomised, parallel group clinical investigation is designed as a superiority study with two primary statistical aims:

1. To demonstrate that the combined endpoint of infection/inflammation, overgrowth, pain and numbness will be significantly lower in the group with the minimally invasive surgical procedure in combination with the use of the BA400 abutment compared to the traditional surgical procedure and BA300 abutment.
2. To demonstrate that the minimally invasive surgical procedure in combination with the use of the BA400 abutment is associated with a significant reduction in direct medical costs, due to shorter surgical procedures, faster wound healing and less complications compared to the traditional surgical procedure in combination with the use of the standard BA300 abutment.

The secondary statistical aims are to show that the minimally invasive surgical procedure in combination with the use of the BA400 abutment is associated with a significant:

- reduction in infection/inflammation evaluated by Holgers Index
- reduction in overgrowth evaluated by the Soft tissue thickening/overgrowth scale
- reduction in time for wound healing evaluated as number of dressings
- reduction in numbness
- reduction in pain in the scar area and neuropathic pain
- reduction in surgery time
- improvement in the aesthetics

2.2 Study Design

The investigation is designed as an international multicentre, open, randomised, comparative, parallel group, prospective clinical investigation. It is a one year investigation with a two year follow-up.

Procedures and timing	Visit 1 Baseline	Visit 2 Surgery	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10
Day/Week/Month ¹	Before day of surgery	D 0	D 10	W 3	W 6	W 12	W 24	M 12	M 24	M 36
Time window			± 4d	± 1w	± 1w	± 2w	± 4w	± 4w	± 6w	± 6w
Demographics	X									
Medical history	X									
Eligibility criteria	X									
Informed consent	X									
Randomisation		X								
Skin thickness		X								
Length of abutment		X								
Implant surgery		X								
Time to perform surgery		X								

Implant stability		X	X	X	X	X	X	X	X	X
Suture removal			X							
Wound healing			X	X	X	X	X			
Baha installation				X						
Use of sound processor ²					X	X	X	X	X	X
Change of abutment			X	X	X	X	X	X	X	X
Loss of implant			X	X	X	X	X	X	X	X
Holgers index			X	X	X	X	X	X	X	X
Soft tissue thickening/overgrowth			X	X	X	X	X	X	X	X
Visible abutment length			X	X	X	X	X	X	X	X
Aesthetic evaluation surgeon						X		X		X
Aesthetic evaluation incl. pain question (POSAS) ³						X		X		X
Pain ^{2,3}			X	X	X		X			
Numbness			X	X	X	X	X	X	X	X
Use of nicotine ²	X			X		X		X	X	X
Health Utilities Index ²	X						X	X		X
Abbreviated Profile of Hearing Aid Benefit ²	X						X	X		X
Extra visits			X	X	X	X	X	X		
Concomitant treatment			X	X	X	X	X	X		
Concomitant medication			X	X	X	X	X	X		
Device deficiency		X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X		
ADE									X	X
Health care costs ⁴	X	X	X	X	X	X	X	X	X	X

¹ The time between visits will be calculated from visit 1 (time 0)

² To be completed by subject on questionnaires

³ Pain question included in the POSAS scale

⁴ This is not specified like this in the protocol but added here to clarify that we measure Health care costs related to the procedure throughout the study

2.3 Treatment Groups

Subjects were randomised to either:

- Test group: Minimally invasive surgery and use of a BA400 abutment.
- Control group: Standard surgery and use of a BA300 abutment.

2.4 Sample Size

Sample size calculations were performed for both primary analyses. The significance level of 0.05 is split between the two primary analyses: combined endpoint 0.0499 and direct medical cost 0.0001.

2.4.1 Sample size calculation for the combined endpoint of infection/inflammation, overgrowth, pain and numbness

It is estimated that the distribution of the number of events regarding infection/inflammation, overgrowth, pain and numbness with the traditional surgical procedure and BA300 abutment is as follows; 60% no events, 18% one event, 12% two events, 7% three events and 3% four

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events. In order to achieve a power of 80% with the Mantel-Haenszel two-sided chi-square test at significance level of 0.0499 when the distribution of the number of events with the new surgical procedure and new abutment BA400 is as follows; 81% no events, 13% one event, 5% two events, 1% three events and 0% four events 50 statistical evaluable subjects are needed in each group. The sample size calculation is based on 10000 simulated studies.

2.4.2 *Sample size calculation for direct medical costs, based on time for surgical procedures, wound healing and complications*

The power that is achieved if the previously needed 50 statistical subjects in each group are used for the economic evaluation is calculated as follows: From a 12 months prospective follow-up by Hultcrantz¹ the mean time required for surgery was 44.57 (SD 7.41) minutes with skin reduction and 28.14 (SD 3.67) minutes without skin reduction. If a normal distribution of the time required for surgery, 15% infection/inflammation and 15% extra dressings with skin reduction, versus 9% infection/inflammation and 10% extra dressings without skin reduction, a power of more than 99% with the two-sided Mann-Whitney U-test at a significance level 0.0001 would be achieved. The sample size calculation is based on 10000 simulated studies.

In order to compensate for a drop-out rate of 5% we needed to randomize 53 subjects to each group.

3 STUDY POPULATIONS

3.1 Definition of Study Populations

3.1.1 *Intent-to-Treat Population (Full Analysis Set)*

The Intent to Treat population (ITT) consists of all randomised patients with at least one follow-up measurement from visit 3 Day 10 and onward.

3.1.2 *Per-Protocol Population*

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

3.1.3 *Safety Population*

The safety population consists of all surgically treated patients, grouped after surgical procedure.

4 STUDY VARIABLES

4.1 Baseline Variables

4.1.1 *Demographics and Baseline Characteristics*

- Age at Baseline (Date of Baseline visit - Date of birth)
- Gender (Male/Female)
- Ethnical background (American Indian/Alaska Native, Asian (East Asia), Black, Hawaiian/Pacific Islander, White (Caucasian))
- Site
- Country
- Use of nicotine/Smoking habits (No, Smoking - Less than 10 cigarettes/day, Smoking - Between 11 and 20 cigarettes/day, Smoking - Between 21 and 40 cigarettes/day, Smoking - More than 40 cigarettes/day)
- Snuff (Yes/No) and number of cans per month (for Swedish patients only)

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- Type of hearing loss (conductive or mixed hearing loss or single-sided sensorineural deafness)

4.1.2 Medical and Surgical History

Relevant medical and surgical history as judged by the investigator will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

4.1.3 Prior and Concomitant Medications

Prior and concomitant medication will be coded according to the Anatomic Therapeutic Chemical classification system (ATC).

4.2 Efficacy Variables

4.2.1 Primary Clinical Efficacy Variable

The first **primary endpoint, a combined endpoint of infection/inflammation, overgrowth, pain and numbness will be evaluated**, as the sum of the following four events:

1. Holgers Index ≥ 2 any time between 3 weeks visit to 1 year at a visit or recorded on the AE page from day 21/3 weeks visit to day 365/1 year visit
2. Any overgrowth (≥ 2) any time between 3 weeks to 1 year
3. Pain (scar/neuropathic) according to POSAS ≥ 3 or pain questions in CRF ≥ 3 any time between 3 weeks to 1 year
4. Any numbness any time between 3 weeks to 1 year

4.2.2 Primary Economical Efficacy Variable

The second primary endpoint: **direct medical cost** associated with the surgery (time to perform surgery, number of wound dressings sessions and cost to treat complications) during the first year will be calculated for each subject using standard cost/unit for each participating country. This means that the direct medical costs are all health care costs, incurred, related to the procedure. The following subsection will define the guidelines for creating the direct medical cost tabulation.

4.2.2.1. Cost identification

All measured costs relating to the procedure and its complications will be identified and tabulated. In case of doubt, an independent physician will decide if certain costs should be included. The costs include, but are not limited to:

Surgery:

- The time to perform surgery, "skin to skin" time
- Type of anaesthesia at surgery
- Days in hospital due to surgery

Extra visits caused by wound dressings (check box):

- Number of extra visits due to Wound dressing
- Surgeon conducted the visit multiplied with Duration of extra visit
- Surgical nurse conducted the visit multiplied with Duration of extra visit
- Audiologist conducted the visit multiplied with Duration of extra visit
- Material used (will be listed and cost estimated)

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Extra visits caused by complications (check box):

- Number of extra visits due to Complication
- Surgeon conducted the visit multiplied with Duration of extra visit
- Surgical nurse conducted the visit multiplied with Duration of extra visit
- Audiologist conducted the visit multiplied with Duration of extra visit
- Material used (will be listed and cost estimated)

Concomitant therapy:

- A list of concomitant therapies will be reviewed and therapies identified as related to the surgery/implant and cost estimated. It is of importance that no double reporting of these costs and the material used (extra visit) cost will be made.

4.2.2.2. Estimating unit costs

In order to estimate the total cost of treatment for each subject, the respective quantities of resource use (e.g. surgery time, audiologist time, terra-cortril ointment) will be multiplied by their corresponding unit cost. These costs can differ between centers because of small changes in their practices or because of different unit prices (also see "Different countries").

When calculating the total cost per patient, the individual costs are specified and accumulated.

The unit costs of most items will be obtained from nationally or locally available sources. The study will calculate the costs for one jurisdiction at the time with the full data set of all countries accumulated. This will be done for each country (e.g. the study outcomes in Sweden with 106 subjects etc.).

4.2.2.3. Price year, inflation and discounting

Resources and costs were measured in the year in which they were analyzed. Costs were not revalued. Discounting was not performed because of the time frame being just one year.

4.2.2.4. Currency

All costs will be expressed in Euro's. When other currencies are applicable (Swedish Krona), the exchange rate used will be the exchange rate at the day of the database lock.

4.2.3 Secondary Clinical Efficacy Variables

4.2.3.1. The Holgers Index

The **Holgers Index** is designed to capture signs and symptoms of inflammation or infection at the site of implantation. The scale should be completed at visit 3-10.

The following scale will be used:

- | | |
|---|--|
| 0 | No irritation. Epidermal debris removed, if present |
| 1 | Slight redness. Local temporary treatment, if needed |
| 2 | Red and slightly moist tissue. No granulation formation, local treatment and extra controls as indicated |
| 3 | Reddish and moist; sometimes granulations tissue, revision surgery is indicated |
| 4 | Removal of the abutment / implant necessary due to infection |
| R | Removal of implant for reasons not related to skin problems |

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Holgers Index will also be categorised into 0-1 vs 2-4 (R) and 0 vs 1-4 (R) at each visit.

Max of Holgers Index per patient during the study will also be analysed.

Holgers Index according to AE reporting will also be analysed. If no stop date for an AE with Holgers Index is entered the AE is ongoing and should be counted from the start date and onwards.

4.2.3.2. Soft tissue thickening/overgrowth

In order to capture **soft tissue thickening/overgrowth** the following scale has been developed for this investigation. The scale should be completed at visit 3-10.

The following scale will be used:

- 0 No soft tissue thickening or overgrowth
- 1 Slight soft tissue thickening or overgrowth
- 2 Moderate soft tissue thickening or overgrowth. Local treatment and extra controls as indicated
- 3 Marked/distinct soft tissue thickening or overgrowth. Revision surgery is indicated.

Max of the soft tissue thickening/overgrowth will be calculated for each patient.

4.2.3.3. Wound healing

At visit 3-7 determination if the **wound is healed or not** will be performed.

The **visible abutment length** will be measured at visit 3-10 and change from visit 3 will be calculated.

4.2.3.4. Aesthetic outcomes

The **aesthetic outcome** of the surgery will be evaluated by the subject and the surgeon at visit 6, 8 and 10. The scar will be evaluated in accordance with the Patient and Observer Scar Assessment Scale (POSAS) v 2.0 that consists of two parts, a patient scale and an observer scale:

- Patient items:
 - pain
 - itching
 - colour
 - stiffness
 - thickness
 - irregularity
 - overall opinion
- Observer items:
 - vascularity
 - pigmentation
 - thickness
 - relief
 - pliability
 - surface area and
 - overall opinion

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4.2.3.5. Pain

At visits 3, 4, 5 and 7 the **pain** questions “Has the scar been painful the past few weeks?” and “Any neuropathic pain during the past weeks?” will be evaluated. At visit 6, 8 and 10 the pain questions in the POSAS observer scale will be used.

Pain (2 variables) will also be analysed in a categorical manner: 1, 2-3, 4-6 and 7-10.

Max pain (2 variables) per patient will be analysed.

Max pain (2 variables) will also be analysed in a categorical manner: 1, 2-3, 4-6 and 7-10.

4.2.3.6. Numbness

Subjects will be asked if they experience any **numbness** (No numbness, Numbness within 2 cm from the abutment, Numbness within and beyond 2 cm from the abutment) around the abutment at visit 3-10.

Also **Max of the numbness score** for each patient will be analyzed.

4.2.3.7. Surgical time

Surgical time (min) will be analysed.

4.2.4 Secondary Economical Efficacy Variables

4.2.4.1. Direct medical costs by component

The components (Surgery, Wound dressings, Complications and Concomitant therapy) of **Direct medical costs** will also be analysed.

4.2.5 Tertiary Clinical Efficacy Variables

The **Health Utilities Index (HUI-III)** dimensions (3-6 levels) and HRQL (Hearing related quality of life) score at visit 1, 7, 8 and 10 and change from visit 1:

- vision
- hearing
- speech
- ambulation/mobility
- pain
- dexterity
- self-care
- emotion and
- cognition

Coding will proceed according to the HUI-III coding and procedure manual². The attribute levels, single-attribute utility scores, overall health-state vector and overall HRQL utility scores will be calculated according to this instruction.

4.2.5.1. APHAB

Abbreviated Profile of Hearing Aid Benefit (APHAB), unaided and aided, scores at visit 1 (only unaided), 7 8, and 10 and difference between aided at visit 7, 8 and 10 and unaided at visit 1 will be computed:

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- Ease of Communication
- Reverberation
- Background Noise
- Aversiveness
- Global Score

4.2.5.2. Sound processor usage

Use of sound processor will be presented at visit 5 to 10:

- Number of hours per week will be calculated from the CRF fields Number of days of use per week and Number of hours of use per day
- Type of sound processor used

Non-usage (less than one hour of Baha usage per week) at more than one visit will be analysed.

4.2.5.3. Implant stability

Implant Stability Quotient (ISQ) High and Low will be presented at surgery as a baseline value and at visit 2-10. Change from Surgery will also be calculated. Mean ISQ AUC₀₋₁₂ months, Mean ISQ AUC₀₋₂₄ months and Mean ISQ AUC₀₋₃₆ months will be calculated for subjects without abutment changes.

4.2.5.4. Smoking habits and snuff

Smoking habits (No, Smoking - Less than 10 cigarettes/day, Smoking - Between 11 and 20 cigarettes/day, Smoking - Between 21 and 40 cigarettes/day, Smoking - More than 40 cigarettes/day) at visits 1, 4, 6, 8, 9 and 10.

Snuff (Yes/No) and number of cans per month (for Swedish patients only) at visits 1, 4, 6, 8, 9 and 10.

4.2.5.5. Additional surgical variables

Additional information recorded during **surgery**:

- Type of surgery
- Skin thickness (test group only)
- Length of the abutment

4.2.5.6. Variables for the cost consequence analysis

- HUI-III utility scores will be calculated before surgery, at 24 weeks, at 12 months after surgery. The HUI-III QALY over 1 year will be calculated using the following AUC method: multiplying the average utility of two subsequent measurements with the time interval, and adding up over both time intervals. In case of missing values prior to surgery, the mean of patients with a similar aetiology (SSD, mixed, conductive) will be used. In case of a missing value at 6 months, this will be interpolated with the 1 year value. In case of a missing value at 1 year, the last observation carry forward (LOCF) technique will be used. In case of extra measurements, these will be added to the AUC calculation. In case of an implant and/or permanent abutment extrusion or removal, the last unaided HUI-III will be used to portray the last health state without the Baha, unless an extra HUI-III was performed to portray this health state.
- The unaided Global APHAB score before surgery and afterwards aided global APHAB score over the first year (AUC) will be calculated per patient. In case of

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missing values prior to surgery, the mean of patients with a similar aetiology (SSD, mixed, conductive) will be used. In case of a missing value at 6 months, this will be interpolated with the 1 year value. In case of a missing value at 1 year, the LOCF technique will be used. In case of extra measurements, these will be added to the AUC calculation. In case of an implant and/or permanent extrusion or abutment removal, the last unaided APHAB global score will be used.

- The POSAS before surgery can be presumed to be the lowest value (1) and afterwards the POSAS over the first year (AUC) will be calculated per patient. Same imputation rules as in APHAB and HUI-III will be made here.
- The course of adverse soft tissue reactions will be calculated over the first year (AUC) per patient as measured by the Holgers Index taken from AE page and from visits. The Holgers index will be carried forward up to next change of Holgers index (at an ordinary visit or an extra visit due to an AE with Holgers). AUC (y =Holgers severity (0-4), x =day 0 - 365). If no stop date for an AE with Holgers Index is entered, the AE is ongoing and should be counted from the start date and onwards. Sensitivity analyses of the carry forward for of Holgers from visits and onward will be made as required.

The AUC of the APHAB and HUI-3 will be calculated using the assumption that the health state before and after surgery is similar until the audiological fitting occurred with the Baha. The individual Baha fitting time will be used to compensate for the variability in centers. After fitting the average will be calculated between this time point and 4 weeks later (which will be imputed with the value of 24 weeks). The time point between 24 weeks and 1 year will also be averaged. This accumulates to the AUC of the first year.

4.3 Safety Variables

- Time to Loss of implant
- Adverse Events
 - Adverse Event (AE)
 - Adverse Device Effect (ADE), defined as AE with Probably or Definitely related to Study product
 - Serious Adverse Event (SAE)
 - Serious Adverse Device Effect (SADE), define as SAE with Probably or Definitely related to Study product
- Device deficiency by visit and divided by Not leading to SAE, Did lead to SAE and could have led to SAE.
- Removal of abutment

5 STATISTICAL METHODOLOGY

5.1 General Methodology

Continuous variables will be presented with Mean, Standard deviation (SD), 95% confidence interval (CI), Median, Min, Max and number of measures for both treatment groups and categorical variables will be presented with number and percentage.

Information about the methods used for the statistical testing can be found in the paragraphs below.

The primary analyses will be performed on the ITT population and the secondary and tertiary efficacy analyses will be performed on ITT and PP populations. The exploratory analyses are only performed for ITT population. Safety analyses will be performed on the safety population.

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In case of significant amount of missing data, sensitivity analyses will be performed. Imputations will be made in the most appropriate way and the techniques used will be similar in the two groups. In case of disagreement between relevant parties, an independent expert will be consulted to ascertain that the method of imputation does not benefit or inhibit one group over the other.

The significance level of 0.05 will be split between the two primary analyses: combined endpoint 0.0499 and direct medical cost 0.0001. All other tests will be two-tailed and conducted at 0.05 significance level. All analyses will be performed by using SAS® v9.4 (Cary, NC).

5.2 Patient Disposition and Data Sets Analyzed

The number of subjects included in each of the ITT, PP and Safety populations will be summarised for each treatment group and overall. The number and percentage of subjects randomised and treated will be presented. 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.

5.3 Protocol Violations/Deviations

Major protocol deviations are those that are considered to have an effect on the analysis. A list of potential major protocol deviations will be generated programmatically from the data captured before the clean file meeting. The clinical monitors of the study will review the list and the finalisation of the major protocol deviations will be done at the clean file meeting. The number of patients with major protocol deviations will be summarised per treatment group.

5.4 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarised by treatment group for the ITT and PP populations. Continuous variables will be tested with Mann-Whitney U-test between the two groups, dichotomous variables with Fishers exact test, ordered categorical variables with Mantel-Haenszel Chi-square test and non-ordered categorical variables with Chi-square test. Site and country will not be tested between treatments.

5.5 Medical and Surgical History

Medical and surgical history will be summarized by System Organ Class (SOC) and Preferred Term (PT) for each treatment group for the ITT population. No statistical testing will be done.

5.6 Prior and Concomitant Medications

Prior and concomitant medication will be summarised by higher level anatomical therapeutic classification (ATC) group and generic term for each treatment group for ITT population. No statistical testing will be done.

5.7 Efficacy Analyses

5.7.1 Primary Efficacy Analysis

5.7.1.1. Clinical analysis

The combined primary variable will be analysed by the Mantel-Haenszel Chi-square test. The variable will be summarised in a table as a categorical variable. A stacked bar chart (up to

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100%) with one bar per treatment group will be produced. A plot of individual values of Holgers Index, Overgrowth, Pain (scar/neuropathic) according to POSAS or pain questions in CRF and Numbness with patient number on the y-axis and time (3 weeks to 1 year) on x-axis. The individual values will be shown as different symbols at each visit to indicate level of complication.

5.7.1.2. Cost analysis

The mean total costs per group will be presented and the difference analyzed using a t-test, if the data is normally distributed. In case of skewed data bootstrapped 95% CI will be presented. Medians will be presented, and the difference will be tested using the Mann-Whitney U test.

5.7.2 Secondary Efficacy Analyses

The combined variable used in the primary analysis will also be analysed in the same way but for PP population and also only for subjects who completed all visits in the study.

The distribution of Holgers Index will be tested between treatment groups with Mantel-Haenszel Chi-square test at each visit. Holgers index by visit will also be presented in a figure. Max of Holgers Index per patient will be tested in the same way but only once and not per visit. The distribution of all Holgers Index values over all visits will be presented but no testing of this will be done.

Holgers Index according to AE reporting will be analysed by:

- Plot the incidence rate Holgers ≥ 2 per day over time
- Plot individual patient Holgers Index values using boxes/bars indicated by different colours by severity with patients on y-axis and calendar time on x-axis.
- The distribution of all Holgers Index values over all AEs will be presented by treatment group but no testing of this will be done.
- Plot visit Holgers data and movement between visits by treatment group.

The distribution of soft tissue thickening/overgrowth will be tested between treatment groups with Mantel-Haenszel Chi-square test at each visit.

The number of resources and costs of the components Direct medical costs will be summarised by treatment groups. The costs of the 3 components: surgery, wound dressing and complications will be tested between groups by using Mann-Whitney U test.

Wound healing will be tested between treatment groups by visit with Fishers exact test.

The visible abutment length and change from visit 3 will be tested between groups by visit by using Mann-Whitney U test. This test will only be done for patients with no change of abutment. For patients with an abutment change spaghetti plots will be created of the visual abutment length over time with indication of when abutment change is made and an indication of length of the new abutment.

The aesthetic outcome (POSAS) scales and the two pain questions will be tested between groups by visit by using Mann-Whitney U test.

The distribution of numbness will be tested between treatment groups with Mantel-Haenszel Chi-square test at each visit.

Surgery time will be tested between groups by using Mann-Whitney U test.

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5.7.3 Tertiary Efficacy Analyses

Holgers Index according to AE reporting will be analysed by:

- Plot the mean Holgers Index per day and treatment group

Health Utilities Index (HUI-III) dimensions and overall score will be tested between groups by using Mann-Whitney U test by visit. The Health Utilities Index (HUI-III) QALY will be tested between groups by using Mann-Whitney U test.

APHAB will be tested between groups by using Mann-Whitney U test by visit. The APHAB global score AUC will be tested between groups by using Mann-Whitney U test.

Use of sound processor will be calculated for those who used a processor. Number of hours per week will be tested between groups by using Mann-Whitney U test by visit. Type of sound processor used at a visit will be presented with number and percentage (no statistical testing).

Absolute ISQ High and Low values will be presented by visit and abutment length. Patients can change abutment length during the study. Change in ISQ High and ISQ Low and AUC analysis will be made by visit for all patients and also for patients without change of abutment length during the study. Test between groups will be performed using Mann-Whitney U-test.

Smoking habits (No, Smoking - Less than 10 cigarettes/day, Smoking - Between 11 and 20 cigarettes/day, Smoking - Between 21 and 40 cigarettes/day, Smoking - More than 40 cigarettes/day) will be presented by visit and between groups will be performed using Mantel-Haenszel Chi-square test at each visit.

Type of surgery will be tested between groups using Fishers exact test.

Skin thickness (test group only) will only be described descriptively.

Length of the abutment will be described with frequencies between groups. No statistical testing will be done.

Cost consequence analysis between treatment groups will be made. HUI-III (QALY), APHAB, POSAS and Holgers Index AUC will be used together with the total cost. Estimates per treatment group and for the difference between groups with 95% CI will be presented. Additional analyses per SSD, Conductive and Mixed and per country and site will be presented.

5.7.4 Exploratory Clinical Efficacy Analyses

The following exploratory clinical efficacy variables will be *considered* for analysis. In case an analysis is performed, the results will be presented.

5.7.4.1. Holgers Index

The course of peri-abutment dermatitis will be calculated over the first year (AUC) per patient as measured in the Holgers Index taken from AE page and from visits for both groups. The AUC will be created by a predefined set of assumptions and rules. A sensitivity analysis will be conducted to assess the impact of these assumptions (worst/best case scaling).

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5.7.4.2. Skin thickness/overgrowth

It is assumed that skin overgrowth is related to peri-abutment dermatitis. This would lead to a relation between the AUC of peri-abutment dermatitis and the skin thickness/overgrowth scale.

5.7.4.3. Pain

The area under the curve will be calculated for both groups of both pain attributes. This variable will be used in mixed models for hypothesis generating purposes.

5.7.4.4. Numbness

A mixed model will be created to investigate if numbness is related to pain for hypothesis generating purposes.

5.7.4.5. Aesthetic outcomes

The POSAS has been used in this study, but for Baha, no clinically relevant thresholds have been defined. An exploratory analysis using cluster analysis will be used to estimate the most clinically relevant thresholds and dimensions for the patient and observer outcomes.

5.7.4.6. Implant stability (ISQ)

A mixed model and/or cluster analyses will be performed for the different abutment types and lengths to determine what the normal clinical course of ISQ development is after surgery. This will possibly result in clinically relevant ISQ values.

5.7.4.7. Implant extrusion

Implant extrusion is clinically not expected to occur at random. We clinically can define two important periods, the period of osseointegration (up to three months) and the time after this period. Using a modelling approach, the incidence densities for implant extrusion will be calculated within these two period for hypothesis generating purposes.

5.7.4.8. APHAB

The mean benefits for the subscales will be presented together with the corresponding normalized percentiles for both the unaided and aided scores for both groups for hypothesis generating purposes. Also it will be investigated if a response shift is present during the first year.

5.7.4.9. Type of surgery

For the control group, two separate techniques (c-shape/linear) can be used. The relative amounts will be expressed.

5.7.4.10. Smoking

Smoking habits (No, Smoking - Less than 10 cigarettes/day, Smoking - Between 11 and 20 cigarettes/day, Smoking - Between 21 and 40 cigarettes/day, Smoking - More than 40 cigarettes/day) at visits 1, 4, 6, 8, 9 and 10. For hypothesis generating purposes, a mixed model will be created using the primary outcome and smoking as measured during this study in the first year.

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5.7.4.11. *Per site analyses*

Any previous specified analyses may be performed per site.

5.8 Safety Analyses

5.8.1 *Loss of implant*

The loss of implants will be analysed with the Log-rank test between the two treatment groups and illustrated with Kaplan-Meier survival curves. The survival probabilities at 90 days, 180 days and at 365 days (from the KM-estimates) will be tabulated. Cox proportional Hazard ratio (with 95% CI) of implant loss for treatment group will be presented. Number of loss of implant and total follow up time per treatment group will be presented. Based on these numbers simulations (Markov-Modelling) of different scenarios will be made.

5.8.2 *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 treatment-related AE (Probably + Definitely)
- Any treatment-related SAE (Probably + Definitely)
- Death

Summaries per System Organ Class (SOC) and Preferred Term (PT) presenting n of AEs and n (%) of subjects with at least one AE will be provided for:

- All AEs (includes all serious and non-serious AEs)
- All AEs by Severity
- All AEs by Relation to Treatment
- All SAEs

5.8.3 *Device deficiency*

Number of Device Deficiencies and number and percentage of patients with a Device Deficiency.

5.8.4 *Removal of abutment*

Number and percentage of removal of abutment will be presented by treatment group.

6 INTERIM ANALYSES

The main analysis will be after 12 months of follow-up and updated follow-up analysis after 3 years.

7 CHANGES OF ANALYSIS FROM PROTOCOL

The primary economical variable is defined as the following in the protocol:

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“direct medical cost associated with the surgery (time to perform surgery, number of wound dressings sessions and cost to treat complications)”

It is now changed to be able to include more costs and is now defined as:

“direct medical cost associated with the surgery (all health care costs, incurred, related to the procedure)”

8 LISTING OF TABLE, FIGURES AND LISTINGS

8.1 Listing of Tables

Table Number	Table Title
14.1.1	Patient Disposition and Data Sets Analyzed (ITT Population)
14.1.2	Protocol Deviations (ITT Population)
14.1.3.1	Demographics and Baseline Characteristics (ITT Population)
14.1.3.2	Demographics and Baseline Characteristics (PP Population)
14.1.4	Medical and Surgical History (ITT Population)
14.1.5.1	Prior Medications (ITT population)
14.1.5.2	Concomitant Medications (ITT population)
14.2.1.1	Primary Efficacy Analysis (ITT Population)
14.2.1.2	Combined endpoint (PP Population)
14.2.2.1.1	Holgers index by visit (ITT population)
14.2.2.1.2	Holgers index summary analyses (ITT population)
14.2.2.1.3	Soft tissue thickening/overgrowth by visit (ITT population)
14.2.2.1.4	Resources and costs of the components Direct medical costs (ITT population)
14.2.2.1.5	Wound healing by visit (ITT population)
14.2.2.1.6	Visible abutment length by visit for patients with no change of abutment (ITT population)
14.2.2.1.7	Change in visible abutment length from visit 3 by visit for patients with no change of abutment (ITT population)
14.2.2.1.8	POSAS by visit (ITT population)
14.2.2.1.9	POSAS summary analyses (ITT population)
14.2.2.1.10	Numbness by visit (ITT population)
14.2.2.1.11	Numbness summary analyses (ITT population)
14.2.2.1.12	Surgery variables (secondary and tertiary variables) (ITT population)
14.2.2.2.1	Holgers index by visit (PP population)
14.2.2.2.2	Holgers index summary analyses (PP population)
14.2.2.2.3	Soft tissue thickening/overgrowth by visit (PP population)
14.2.2.2.4	Resources and costs of the components Direct medical costs (PP population)
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14.2.2.2.8	POSAS by visit (PP population)
14.2.2.2.9	POSAS summary analyses (PP population)
14.2.2.2.10	Numbness by visit (PP population)
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14.2.2.2.12	Surgery variables (secondary and tertiary variables) (PP population)
14.2.3.1.1	Health Utilities Index (HUI-III) by visit (ITT population)
14.2.3.1.2	APHAB by visit (ITT population)
14.2.3.1.3	Use of sound processor by visit (ITT population)
14.2.3.1.4	Implant stability (ISQ) by visit (ITT population)
14.2.3.1.5	Smoking habits by visit (ITT population)
14.2.3.1.6	Cost consequence analyses HUI-III (QALY), APHAB, POSAS and Holgers Index AUC will be used together with the total cost (ITT population)
14.2.3.2.1	Health Utilities Index (HUI-III) by visit (ITT population)
14.2.3.2.2	APHAB by visit (ITT population)
14.2.3.2.3	Use of sound processor by visit (ITT population)
14.2.3.2.4	Implant stability (ISQ) by visit (ITT population)
14.2.3.2.5	Smoking habits by visit (ITT population)
14.2.3.2.6	Cost consequence analyses HUI-III (QALY), APHAB, POSAS and Holgers Index AUC will be used together with the total cost (ITT population)
14.2.4.x	Exploratory analysis (ITT population)
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14.3.2.1	Summary of Adverse Events (Safety Population)
14.3.2.2	Adverse Events, by System Organ Class and Preferred Term (Safety Population)
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14.3.2.5	Serious Adverse Events, by System Organ Class and Preferred Term (Safety Population)
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8.2 Listing of Figures

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14.2.1	Bar chart of Holgers Index by visit (ITT population)
14.2.2	Incidence rate Holgers Index ≥ 2 per day over time (both AE and visit Holgers Index) (ITT population)
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14.2.4	Mean Holgers Index per day over time (both AE and visit Holgers Index) (ITT population)
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14.2.6	Individual patient Holgers Index values over time (ITT population)
14.2.7	Holgers at visits and movement between visits by treatment groups (ITT population)
14.3.1	Line plot of visual abutment length over time (ITT patients with abutment change)
14.4.1	Bar chart of Overgrowth by visit (ITT population)

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14.5.1	Bar chart of Pain (scar/neuropathic) by visit (ITT population)
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8.3 Listing of Listings

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16.2.7	Adverse Events
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16.2.9	Device deficiency

9 REFERENCES

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10 APPENDIX

None