Clinical Investigation Plan (CIP)

Investigation code	CBAS5439
Version	Final
Version date	19-SEP-2013

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

An international multicentre, open, randomised, comparative, parallel group, prospective clinical investigation.
1 year investigation with a 2 year follow-up

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Sponsor	Cochlear Bone Anchored Solutions AB Konstruktionsvägen 14 PO Box 82 SE-435 22 Mölnlycke Sweden

Investigational sites

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A change to this section does not require a protocol amendment.

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A change to this section does not require a protocol amendment.

Synopsis

Name of sponsor	Cochlear Bone Anchored Solutions AB
Investigation code	CBAS5439
Investigational title	**Clinical and health economic evaluation with a new Baha abutment design combined with a minimally invasive surgical technique**
Design	An international multicentre, open, randomised, comparative, parallel group, prospective clinical investigation. 1 year investigation with a 2 year follow-up
Investigational device(s)	Cochlear™ Baha® BA400 Abutment pre-mounted on Cochlear™ Baha® BI300 4 mm implant
Comparator(s)	Cochlear™ Baha® BA300 Abutment pre-mounted on Cochlear™ Baha® BI300 4 mm implant
Primary objectives	• To demonstrate that the minimally invasive surgical procedure in combination with the use of the BA400 abutment is associated with a reduction of inflammation/ infection, overgrowth, pain and numbness at the site of implantation compared to the traditional surgical procedure in combination with the use of the standard Baha abutment (Cochlear™ Baha® BA300 Abutment). • To demonstrate that the minimally invasive surgical procedure in combination with the use of the BA400 abutment is associated with a 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 Baha abutment (Cochlear™ Baha® BA300 Abutment).

Secondary objective(s)	• To demonstrate that the new surgical procedure and use of the BA400 in comparison with traditional surgical procedure and the use of BA300, is associated with:
	
	  • Less symptoms of inflammation and infection (Holgers index)
	  • Less tissue thickening/overgrowth
	  • Less pain
	  • Less numbness
	  • Faster wound healing
	  • Better aesthetic
	  • Shorter surgical procedures
	
	• Safety evaluation (loss of implant, adverse events and device deficiency)

Tertiary objective	To demonstrate that subjects experience an improved quality of life when receiving a Baha.
Duration of subjects participation	3 years
Investigation period	First Subject First Visit Q4 2012 Last Subject Last Visit Q1 2017
Inclusion criteria	• Adult patient, i.e. ≥ 18 years of age • Eligible for the Baha system • Signed informed consent
Exclusion criteria	• Patient scheduled for simultaneously bilateral implant surgery • Uncontrolled diabetes as judged by the investigator • Condition that could jeopardize osseointegration and/or wound healing, e.g. osteoporosis, psoriasis and use of corticosteroids • Unable to follow the cleaning instruction • Unable to follow investigational procedures, e.g. to complete quality of life scales • Participation in another investigation with pharmaceuticals and/or device • Condition that may have an impact on the outcome of the investigation as judged by the investigator • Suitable implant position for the 4 mm implant not found during surgery due to insufficient bone quality and/or bone thickness
Number of subjects	100 evaluable subjects (in order to compensate for a drop-out rate of 5%, 53 subjects will be randomised to each treatment group). Randomisation in proportion 1:1
Primary endpoint(s)/assessment(s)	The first primary endpoint, a combined endpoint of infection/inflammation, overgrowth, pain and numbness,will be evaluated by a function of the Holgers Index, the Soft tissue thickening/over-growth scale, POSAS pain scale, question regarding pain in scar/neuropathic pain and Numbness scale. The second primary variable, the costs of the surgical procedure, complications and number of extra wound dressings sessions will be evaluated by surgical time, Holgers Index and the number of extra dressing sessions. The costs will be estimated and evaluated in local currency.
Secondary endpoints/assessments	• Wound healing • Numbness • Pain • Aesthetics • Complications • Overgrowth Quality of Life

Safety variable(s)	• Loss of implant • Adverse events • Device deficiency
Statistical methods	The first combined primary variable will be analysed by the Mantel-Haenszel Chi-square test and the cost by the Mann-Whitney U-test between the two groups

Flow chart - see below

Flow chart

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			X
Numbness			X	X	X	X	X	X	X	X
Use of nicotine[2]	X			X		X		X	X	X
Health Utility 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

[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

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Abbreviations

ADE	Adverse Device Effect
AE	Adverse Event
APHAB	Abbreviated Profile of Hearing Aid Benefit
Baha	Bone anchored hearing device
BCI	Bone Conduction Implants
CIP	Clinical Investigation Plan
CRF	Case Report Form
HRQL	Health-Related Quality of Life
HUI	Health Utility Index
ID	Investigational Device
ITT	Intention To Treat
ISO	International Organization for Standardization
ISQ	Implant Stability Quotient
MDD	Medical Device Directive
MedDRA	Medical Dictionary for Regulatory Activities
POSAS	Patient and Observer Scar Assessment Scale
PP	Per Protocol
PT	Preferred Term
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
USADE	Unanticipated Serious Adverse Device Effect

1 Introduction

1.1 Background

1.1.1 Clinical experience with Baha

Bone conduction implants (BCI) such as the Baha® system were first clinically described in 1977 by Tjellström et al.[1], and since then more than 80 000 patients have been treated with this technique.

The Baha system consists of a titanium implant, which is integrated with the bone tissue of the skull and is connected to an external sound processor via a skin penetrating abutment. The sound processor transforms sound to vibrations that are transmitted via the abutment and titanium implant to the skull bone and then to the cochlea.

The surgical procedures that are currently used for Baha surgery make use of a dermatome or scalpel techniques (e.g. linear or C-shaped incisions) to remove subcutaneous tissue down to the periosteum, thus creating a thin, hair-free skin flap. The rationale for skin thinning is to reduce the mobility of the skin surrounding the abutment to minimise the risk for infection or other local skin reactions.

Despite extensive soft tissue reduction, the most common complications associated with Baha implants are related to adverse skin reactions around the abutment. The reduction of the skin also adds complexity to the surgical procedure that is otherwise a routine type of skin incision. A less invasive surgical technique avoiding reducing the thickness of the skin would render a simpler and shorter procedure and would be aesthetically appealing to the patients, as permanent hair removal in the area around the abutment would not be required. Faster healing and less numbness (sensory loss/ paraesthesia) at the implant site may also be expected if the soft tissue thickness is left intact.

1.1.2 Less invasive surgery

Recent published investigations have indicated that good outcomes may be achieved using surgical procedures without skin thinning. In a 12 month prospective follow-up study by Hultcrantz[2], seven patients who underwent surgery without skin thinning using a linear incision technique (test group) were compared to seven age–matched patients who underwent standard surgery with skin thinning using the dermatome technique (control group). The following results were reported:

- The mean time required for surgery was 28.1 and 44.6 minutes for the test and control groups, respectively (p=0.004).
- The wounds of all patients in the test group had healed after 10 days, whereas 71.4% of the patients in the control group required a prolonged healing period of up to two months (p = 0.02)
- One patient in the test group showed an adverse tissue reaction compared to three patients in the control group
- Numbness was reported by one patient in the test group at 12 months compared to six patients in the control group
- The aesthetic outcome, as judged by the investigator, was reported to be “far better” in the test group compared to the control group

In addition Soo et al.[3] reported on their experience with Baha surgery without soft tissue reduction or skin grafting. Between June 2007 and March 2011, 32 patients had undergone Baha surgery with the new technique, 21 adults and 11 children. Twelve skin reactions were observed. Two fixtures were explanted for clinical and social reasons, and implant loss occurred in one child (age 6) with thin soft

bone. No implant loss due to periabutment infection or periabutment hyperplasia was observed. The authors conclude that this surgical technique appears to have an acceptably low rate of observed skin reactions.

1.1.3 Abutment design and materials

While the above investigations show encouraging outcomes and indicate that sufficient soft tissue stability may be achieved without reducing subcutaneous tissues, it should be noted that, although titanium is known to possess excellent biocompatibility and is widely used as an implant material thanks to its unique ability to osseointegrate in bone, it is not known to integrate firmly in dermal tissues[4]. Findings in the literature indicate that soft tissue stability may be improved by the use of improved abutment designs[5] and/or improved materials. Recent developments in Baha abutment design have shown improved clinical outcomes, in terms of a significant reduction in adverse skin reactions when used with soft tissue reduction, compared to previous generation abutments[19]. Ideally, the Baha abutment should provide conditions for integration with the surrounding soft tissue, thus immobilising the surgical flap, and eliminating/reducing the need for removal of subcutaneous soft tissue.

1.1.4 Cochlear™ Baha® BA400 Abutment

In order to remove the need to perform soft tissue reduction during Baha surgery to improve the cosmetic outcome and further simplify the Baha surgical procedure a new abutment (Cochlear™ Baha® BA400 Abutment) has been developed by Cochlear Bone Anchored Solutions , Mölnlycke, Sweden. The new abutment has a design aimed to improve soft tissue adherence to the abutment and limit pocket formation, which is believed to be key for maintaining good soft tissue health. The abutment has been designed with a concave shape at the lower aspect of the abutment, and the titanium surface has been partly coated with a hydroxyapatite layer.


Cochlear Baha BIA400

The concave shape is believed to be beneficial in stabilising the soft tissue by increasing the length of the soft tissue-to-implant contact and by creating a void space in which a blood clot may form and provide space for new soft tissue regeneration as proposed by Rompen et al[5].

Hydroxyapatite is a well-known biomaterial, which finds its application in different types of medical implants, such as orthopaedic and dental implants. Pre-clinical and clinical investigations on different percutaneous implant devices have shown that hydroxyapatite provides enhanced soft tissue contact thus limiting epidermal down growth and pocket formation (providing a barrier against bacterial infiltration) and stabilising the soft tissue. [6, 7, 8, 9, 10, 11]

1.1.5 Pre-clinical results on hydroxyapatite-coated Baha abutments

A pre-clinical investigation has been performed by researchers at the University of Gothenburg (Sweden) to evaluate the soft tissue response to experimental Baha abutments with and without a hydroxyapatite surface and with and without a pronounced concave shape[18]. The study included 6 adult sheep receiving a total of 36 Cochlear™ Baha® BI300 4mm implants with pre-mounted 9mm abutments of 4 different types: (A) Cochlear™ Baha® BA300 abutment, (B) BA300 abutment coated with hydroxyapatite, (C) concave titanium abutment, and (D) concave titanium abutment coated with hydroxyapatite. The implants and abutments were inserted in the skull without performing soft tissue reduction. The sites were left to heal for 1, 2 and 4 weeks (2 animals per time point) before samples were analysed by descriptive histology and morphometric measurements of pocket depth and epidermal downgrowth.

The histological samples showed tight contact between hydroxyapatite-coated abutments and surrounding soft tissues with minimal epidermal downgrowth and absence of inflammation, while weaker adherence often associated with significant epidermal downgrowth and pocket formation was noted for non-coated titanium abutments. The smallest pocket depth and epidermal downgrowth was recorded for the hydroxyapatite-coated concave abutment (abutment type D) which had the same design as the new BA400 abutment. The mean pocket depth for abutment types A, B, C and D was 1.38 mm (SD 1.22), 0.42 mm (SD 0.75), 1.51 mm (SD 0.69) and 0.24 (SD 0.39), respectively; the difference between C and D was statistically significant (p=0.031). Evaluation of samples with different healing times showed stable—and possibly decreasing—pocket depth for hydroxyapatite-coated between 2 and 4 weeks of healing, while a trend towards increasing pocket depths was noted for non-coated titanium abutments. The presence of a blood clot was noted after 1 week of healing within the concavity of a number of concave-shaped abutments; such histological pattern was not noted on samples with the standard shape. At the later time points, the concavity became filled with soft tissue. This observation is in line with data from the dental literature[5], and suggests that the concave shape may further stabilise the soft tissue by creating a void space where new tissue regeneration can take place, resulting in localised thickening and improved stability of the soft tissue.

In conclusion, the results from the pre-clinical investigation showed improved soft tissue adherence and significantly reduced pocket depth for hydroxyapatite-coated compared to non-coated abutments placed without soft tissue reduction.

1.2 Rationale

The Cochlear™ Baha® BA300 Abutment together with a surgical procedure that includes soft tissue reduction was CE marked in April 2010. The new abutment, Cochlear™ Baha® BA400, together with a surgical procedure that does not require soft tissue reduction was CE marked in June 2012.

The rationale behind this investigation is to make a ‘head-to-head’ comparison between the BA300 and BA400 and the associated surgical techniques in order to get information regarding complications (inflammation/infection, numbness and pain), aesthetic outcome and utilisation of direct medical cost associated with surgery.

1.3 Objectives

1.3.1 Primary clinical objective

To demonstrate that the minimally invasive surgical procedure in combination with the use of the BA400 abutment is associated with a reduction of inflammation/ infection, overgrowth, pain and numbness at the site of implantation compared to the traditional surgical procedure in combination with the use of the standard Baha abutment (Cochlear™ Baha® BA300 Abutment).

1.3.2 Primary economic objective

To demonstrate that the new surgical procedure in combination with the use of the BA400 abutment is associated with a 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 Baha abutment (Cochlear™ Baha® BA300 Abutment).

1.3.3 Secondary objectives

- To demonstrate that the new surgical procedure and use of the BA400 in comparison with traditional surgical procedure and the use of BA300, is associated with:
    - Less symptoms of inflammation and infection (Holgers index)
    - Less tissue thickening/overgrowth
    - Less pain
    - Less numbness
    - Faster wound healing
    - Better aesthetic
    - Shorter surgical procedures

- Safety evaluation (loss of implant, adverse events and device deficiency)

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1.3.4 Tertiary objective

To demonstrate that subjects experience an improved quality of life when receiving a Baha.

2 Statement of compliance

2.1.1 Ethical requirements for the conduct of the investigation

The investigation will be conducted in accordance with the ethical principles as described in the latest version of the Declaration of Helsinki adopted by the World Medical Association.

The Clinical Investigation Plan (CIP), the informed consent form and any other written information that will be given to subjects will be submitted to the appropriate ethics committee.

2.1.2 Regulatory requirements for the conduct of the investigation

The investigation does not need approval from regulatory authorities within EU since the investigational devices are CE marked for the intended use described in this CIP.

The investigation will be conducted in accordance with applicable local regulations, e.g. data protection legislation.

2.1.3 Updates

The appropriate ethics committees shall after initial approval of the investigation receive the following information:

- Status reports and written summary of the investigation as required by the ethics committee
- Documentation required in order to apply for an extension
- Documentation required in order to apply for an amendment to the CIP or the informed consent form
- Report(s) with new information that may affect the safety of the subjects or the conduct of the study

A protocol amendment must be approved by concerned ethics committees and regulatory authorities (if applicable).

2.1.4 Quality standards

The staff at the investigational site and the Sponsor shall follow the guidelines provided in the ISO standard ‘Clinical investigation of medical devices for human subjects – Good clinical practice (ISO 14155:2011)’.

3 Medical device(s) used in and after the investigation

3.1 Investigational device(s) and comparator(s)

3.1.1 Investigational device(s)

3.1.1.1 Description of the investigational device(s)

The investigational devices are CE marked in the EU for the intended use in this CIP.

The Cochlear™ Baha® BA400 Abutment has been designed with a concave shape at the lower aspect of the abutment. The abutment is made of commercially pure titanium and is coated with a hydroxyapatite layer on the entire soft tissue-contacting surface of the abutment up to 3 mm below the top surface (2 mm below the top surface on 6 mm abutments). The coating is applied by a plasma-spray technique and has a thickness of approximately 80 μm.

The abutment is available in four different heights (6 mm, 8 mm, 10 mm and 12 mm, measured from below the implant flange) to accommodate different skin thicknesses:.

The investigational device (Cochlear™ Baha® BA400 Abutment) is available in 4 different lengths (6 mm, 8 mm, 10 mm and 12 mm).

The abutments are intended for patients with conductive or mixed hearing loss or single sided sensorineural deafness. Patients should have sufficient bone quality and quantity to support successful implant placement. The abutments are classified as MDD Class IIb medical devices and are delivered sterile for single use.

The abutments used in the investigation are pre-mounted on Cochlear™ Baha® BI300 4 mm implants. Abutments are also available as separate items, to be used in case of abutment change.

The following CE marked products will be used in the investigation:

Product	Description
93329	BIA400 Implant 4mm with Abutment 6mm
93330	BIA400 Implant 4mm with Abutment 8mm
93331	BIA400 Implant 4mm with Abutment 10mm
93332	BIA400 Implant 4mm with Abutment 12mm
93333	BA400 Abutment 6mm
93334	BA400 Abutment 8mm
93335	BA400 Abutment 10mm
93336	BA400 Abutment 12mm

The abutment is compatible with the CE marked surgical instruments for the Cochlear™ Baha® BI300 implant system.

3.1.1.2 **Manufacturer of investigational device(s)**

Cochlear Bone Anchored Solutions AB, Mölnlycke, Sweden.

3.1.2 Comparator

3.1.2.1 **Description of comparator and justification of the choice**

The comparator devices are CE marked in the EU for the intended use in this CIP.

Standard titanium Baha abutments (Cochlear™ Baha® BA300 Abutment) will be used as comparator. The BA300 abutment is made of commercially pure titanium and is available in two different lengths (6 mm and 9 mm).

The comparator device (Cochlear™ Baha® BA300 Abutment) is available in 2 different lengths (6 mm and 9 mm).

The abutments are intended for patients with conductive or mixed hearing loss or single sided sensorineural deafness. Patients should have sufficient bone quality and quantity to support successful implant placement. The abutments are classified as MDD Class IIb medical devices and are delivered sterile for single use.

The abutments used in the investigation are pre-mounted on Cochlear™ Baha® BI300 4 mm implants. Abutments are also available as separate items, to be used in case of abutment change.

The following products will be used in the investigation:

Product	Description
92127	BIA300 implant 4mm with abutment 6mm
92346	BIA300 implant 4mm with abutment 9mm
92130	BA300 abutment 6mm
92131	BA300 abutment 9mm

3.1.2.2 **Manufacturer of comparator**

Cochlear Bone Anchored Solutions AB, Mölnlycke, Sweden

3.1.3 Other medical device or medication to be used during the investigation

A soft tissue measuring instrument, to be used to facilitate selection of abutment height during surgery, is included in the BA400 system. The device will be CE marked in EU as a Class I product before commencing this investigation.

A drill extender is also included in the BA400 system. The purpose of the drill extender is to improve visibility of the site during drilling. The device will be CE marked in EU as a Class I product before commencing this investigation.

The sound processor that will be installed on the abutment will be provided by the clinic in accordance with local practice.

3.1.4 Treatment after the completion of the investigation

Subjects will be treated according to standard treatment at the clinic after the investigation.

4 Subjects

4.1 Selection of subjects

4.1.1 Inclusion criteria

A subject will be eligible for inclusion in the investigation if he/she meets all of the criteria below:

- Adult patient, i.e. ≥ 18 years of age
- Eligible for the Baha system
- Signed informed consent

4.1.2 Exclusion criteria

A subject will be excluded from participation in the investigation if he/she meets any of the criteria below:

- Patient scheduled for simultaneously bilateral implant surgery
- Uncontrolled diabetes as judged by the investigator
- Condition that could jeopardize osseointegration and/or wound healing, e.g. osteoporosis, psoriasis and use of corticosteroids
- Unable to follow the cleaning instruction
- Unable to follow investigational procedures, e.g. to complete quality of life scales
- Participation in another investigation with pharmaceuticals and/or device
- Condition that may have an impact on the outcome of the investigation as judged by the investigator

- Suitable implant position for the 4 mm implant not found during surgery due to insufficient bone quality and/or bone thickness

4.1.3 Number of subjects

106subjects will be included in the investigation in order to have 100 evaluable subjects. The justification for the number of subjects is described in section ‘Statistical considerations’.

4.2 Subject enrolment and Informed consent

Before a subject is asked to sign an informed consent form an investigator must explain the following to the potential investigational subject :

- The rationale, aims and objectives of the investigation
- Risks and benefits
- Alternative treatments
- Extent of the subject’s involvement
- That the subject can withdraw his/hers consent at any time
- That the confidentiality of patient data will be maintained at all time

The subject must have the possibility to ask any questions. Signed and dated informed consent from potential subjects must be obtained before any investigational procedure can be performed. The

investigator will after informed consent has been obtained, assign a unique enrolment number to the subject.

4.3 Randomisation

Subjects will be randomised to either:

- **Test group**: Minimally invasive surgery and the use of Cochlear Baha BA400 Abutment (investigational device).

  or

- **Control group**: Traditional surgery and the use of Cochlear Baha BA300 Abutment (comparator).

Randomisation will be performed in a proportion 1:1 ratio (test group/control group) at visit 2, i.e. the day of surgery, stratified for site with unknown block size.

Randomisation will be based on optimal allocation using a Web-based application.

If a subject discontinues participation in the investigation (see Section 'Discontinuation') his/her randomisation code/subject number will not be re-used. Discontinued subjects are not allowed to re-enter into the investigation.

4.4 Discontinuation

- Subjects are free to discontinue their participation in the investigation at any time
- Subjects may be discontinued from the investigation at any time at the discretion of the investigator

Subjects who themselves discontinue from the investigation should always be asked about the reason(s) for the discontinuation and the presence of any adverse events. If possible, the subject should always be seen and assessed by an investigator. Any adverse event should be followed up.

4.5 Replacement of subjects

If a subject discontinues participation in the investigation, he/she will not be replaced.

4.6 Insurance

In case of any damage or injury occurring during the participation in the investigation, the Sponsor has contracted an insurance company , Willis, which will cover the liability of the Sponsor, the investigators and other persons involved in the investigation. The Sponsor may use a local insurance company, where applicable, according to national legislation.

5 Design of the clinical investigation

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

5.1 Rationale for the design of the clinical investigation

This investigation is designed to evaluate the approved surgical techniques and the two abutments whit the standard procedures when it comes to fitting the sound processor and the follow-up visits at the clinics remains the same.

The rationale for a one year investigation is that within this time period the initial wound healing has occurred, the patients are used to live with the sound processor and that problems with the scar (inflammation/infection) normally has occurred. In order to collect long-term data a two year follow-up has been added to the initial investigation.

In order to have a fair comparison the patients will be randomised to one of the two treatments.

5.2 Variables

5.2.1 Primary efficacy variables

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 to 1 year
2. Any overgrowth any time between 3 weeks to 1 year
3. Pain (scar/neuropathic) according to POSAS >=3 any time between 3 weeks to 1 year
4. Any numbness any time between 3 weeks to 1 year

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) will be calculated for each subject using standard cost/unit in each participating country.

5.2.2 Secondary efficacy variables

The secondary efficacy variables will be evaluated as follows:

- Infections/inflammations will be evaluated by the Holgers Index
- Soft Thickening/overgrowth scale (0-2)
- Wound healing will be evaluated by the surgeon/surgical nurse.
- Numbness (paraesthesia) – the patients will indicate if they experience numbness and the area where they have the problem on a scale from 0-2.
- Pain in the scar area and neuropathic pain will be evaluated by the patient using ‘The Patient and Observer Scar Assessment Scale (POSAS)’ (1-10)
- Aesthetics will be evaluated by the subject and the surgeon using ‘The Patient and Observer Scar Assessment Scale (POSAS)’(two scales):
  - Patient aesthetic scale (1-10)
  - Observer aesthetic scale (1-10)
- Surgery time (min)

5.2.3 Tertiary efficacy variables

Improved quality of life when receiving a Baha will be evaluated by:

- A generic quality of life scale - Health Utility Index (HUI)
  - HRQL score for overall health
  - Vision score
  - Hearing score
  - Speech score
  - Ambulation/mobility score
  - Dexterity score
  - Self-care score
  - Emotion score
  - Cognition score

- A disease specific quality of life scale - Abbreviated Profile of Hearing Aid Benefit (APHAB)

- Usage of the Baha (sound processor)
- Implant stability (ISQ)
- Visual abutment length

5.2.4 Safety variables

- Loss of implant
- Adverse Events
- Serious Adverse Events
- Device deficiency

5.2.5 Demographics and baseline variables

- Age
- Gender
- Ethnical background
- Medical and surgical history
- Current medications and treatments
- Type of hearing loss
- Skin thickness
- Length of abutment
- Nicotine use

5.2.6 Concomitant medications and treatments

- Use of concomitant medications and nicotine
- Use of concomitant treatments

5.3 Investigational flow chart

Table 1: Flow chart

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 (see 4.3.)		X								
Skin thickness (see 6.1)		X								
Length of abutment (see 6.1)		X								
Implant surgery (see 6.2)		X								
Time to perform surgery		X								
Implant stability		X	X	X	X	X	X	X	X	X
Suture removal (see 6.3)			X							
Wound healing			X	X	X	X	X			
Baha installation (see 6.4)				X						
Use of sound processor[2]					X	X	X	X	X	X
Change of abutment (see 6.5)			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		
Aesthetic evaluation incl. pain question (POSAS) [3]						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 Utility Index[2]	X						X	X		
Abbreviated Profile of Hearing Aid Benefit[2]	X						X	X		
Extra visits (see 6.6)			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

[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

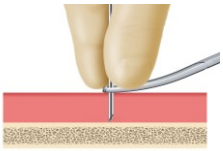
6 Procedures

6.1 Skin thickness and length of abutment

6.1.1 BA300 abutment

The 6 mm pre-mounted abutment on the 4mm implant is for standard use. The 9mm pre-mounted abutment on the 4mm implant is for patients with thicker scalps or if regrowth of subcutaneous tissue is anticipated.

6.1.2 BA400 abutment



The surgeon should measure the tissue thickness before local anaesthesia is infiltrated. A hypodermic needle, a clamp and a ruler may be used. Thereafter an abutment should be selected depending on the tissue thickness

Tissue thickness (mm)	Abutment length (mm)
≤ 4	6
5	8
6	8
7	10
8	10
9	12
10	12
>10	12

6.2 Surgery

Subjects will be randomised to either:

- **Test group:** Minimally invasive surgery and the use of BA400 abutments.

  Selection of abutment length and surgery shall be performed in accordance with the procedure for FAST (one-stage) surgery described in the Surgery Guide.
  In brief, the surgical procedure consists of making a small straight incision through the skin at the planned implant site to access the bone and insert a 4 mm implant with a pre-mounted BA400 abutment of adequate length. After placing the implant and abutment, the incision is sutured back around the abutment ensuring skin edges are everted and in contact with the coated part of the abutment. No removal of soft tissues shall be performed, unless the skin is too thick to accommodate a 12 mm abutment, in which case some adipose tissue may be removed, as described in the Surgery Guide. After closing the incision, suitable dressing and a healing cap shall be used.

  or

- **Control group:** Standard surgery and the use of BA300 abutments.

  Surgery shall be performed in accordance with the procedure for FAST (one-stage) surgery described in the Surgery Guide.
  Soft tissue reduction at the selected implant site shall be performed using either a dermatome technique or a manual technique (e.g. linear or u-shaped incision). The amount of soft tissue removal shall be in accordance with the guidelines provided in the Surgery Guide. A 4 mm implant with a pre-mounted BA300 abutment shall be inserted. The skin flap shall be sutured

back in place ensuring that it sits tight to the bone and periosteum. A biopsy punch may be used to create a hole for the abutment through the skin flap. Wound dressing and healing cap shall be applied following the recommended procedure in the Surgery Guide.

6.3 Removal of sutures

The sutures will be removed at visit 3 (i.e. 10 days after surgery). The surgeon/surgical nurse will determine if the wound requires further wound dressings, and if so, extra visit(s) will be scheduled, until the wound is considered healed.

The subject will receive instruction how to take care of skin around the abutment in accordance with local practice.

6.4 Baha sound processor installation

A Baha sound processor will be installed to the implant at visit 4 (i.e. 3 weeks after surgery). If the wound is not considered sufficiently healed, as judged by the surgeon/surgical nurse, the installation shall be delayed to a scheduled subsequent visit or extra visit, when the site is considered sufficiently healed.

6.5 Change of abutment

If, during the course of the study, the surgeon needs to change the abutment, the subject should receive an abutment in accordance with the randomisation, i.e. test device or comparator.
The type and size of abutment, the reason for the abutment change, and any concomitant treatment and/or medication provided to the subject at the time of abutment change should be recorded in the case report form (CRF).

If the abutment is changed to a longer or shorter abutment during the investigation, ISQ values shall be recorded by resonance frequency analysis according to the procedure described in section 7.3.13

6.6 Extra visit(s)

Extra visit(s) may be a scheduled visit to change the wound dressing or to follow-up any complications. These visits will be recorded on extra pages in the CRF. The following information will be recorded:

- Date
- Reason for extra visit
- Staff that conducted the visit (surgeon, surgical nurse or audiologist)
- Time to perform the visit
- Material used

Subjects will be encouraged to contact the clinic for follow-up if anything out of the ordinary occurs, e.g. local reaction, loss of the implant

7 Assessments

7.1 Subject demographics

The following demographic data will be recorded at inclusion:

- Date of birth (month and year)
- Gender
- Ethnical background
- Use of nicotine

7.2 Medical history

The following subject characteristics will be recorded at inclusion:

- Relevant medical and surgical history as judged by the investigator
- Current concomitant medication and treatments
- Type of hearing loss (conductive or mixed hearing loss or single-sided sensorineural deafness)

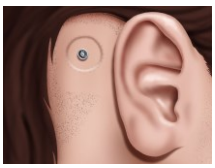
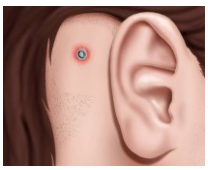
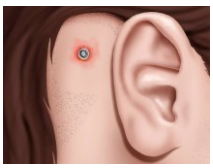
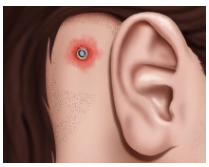
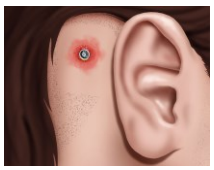
7.3 Efficay variables

7.3.1 Holgers index

The Holgers Index[12] 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*

* Should also be reported on the AE page in the CRF.

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
				

7.3.2 Soft tissue thickening/overgrowth scale

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.*

* Should also be reported on the AE page in the CRF

7.3.3 Direct medical cost

7.3.3.1 Time to perform surgery

The time to perform surgery will be recorded as “skin to skin” time, i.e. the time from first skin incision until finishing suturing the wound. Also the attending staff and type of anaesthesia will be recorded.

7.3.3.2 Number of dressings

The total number of wound dressings performed, i.e. number of extra visits, duration of visit, staff that conducted the visit, and material used.

7.3.3.3 Treatment of complications

All resources used to treat complications will be recorded, e.g. extra visits , type of treatment (e.g. local treatment, re-surgery, etc), and concomitant medication.

7.3.4 Wound healing

A surgeon or a surgical nurse will at visit 3-7 determine if the wound is healed or not healed.

7.3.5 Visible abutment length

The visible abutment length (from skin to top of the abutment) will be measured at visit 3-10 using a ruler. The ruler must be appropriately cleaned before use, by using Isopropanol (99,7%).

7.3.6 Aesthetic evaluation

The aesthetic outcome of the surgery will be evaluated by the subject and the surgeon at visit 6 and 8. The scar will be evaluated in accordance with the Patient and Observer Scar Assessment Scale (POSAS) v 2.0[13] that consists of two parts, a patient scale and an observer scale:

- The patient scale contains six items (pain, itching, color, stiffness, thickness and irregularity) that should be scored 1-10, with 10 indicating the worst imaginable scar or sensation.
- The observer scale also contains six items (vascularity, pigmentation, thickness, relief, pliability and surface area) that should be scored 1-10. Besides the 10-step scale, category boxes are available to score nominal parameters (e.g. type of color).
- Both the patient and the observer should finally score the overall opinion of the scar on the 1-10 scale.

7.3.7 Pain

The pain question available in the POSAS scale will be completed by the subjects also at visit 3, 4, 5 and 7 in addition to visit 6 and 8 when all items will be rated on the POSAS scale.

The subject will rate the following question 'has the scar been painful the past few weeks' on the 1-10 scale were 1= no, not at all and 10=yes, very much.

A second pain question will be added to the POSAS scale 'have you had any neuropathic pain during the past weeks'. The same scale as above applies. Investigational staff will explain the meaning of the term 'neuropathic pain' before the patient will complete the questionnaire.

7.3.8 Numbness

Subjects will be asked if they experience any numbness around the abutment at visit 3-10. The following scale will be used:

1. No numbness
2. Numbness within 2 cm from the abutment
3. Numbness within and beyond 2 cm from the abutment

7.3.9 Health Utilities Index Mark 3 (HUI3)

The Health Utilities Index (HUI®) is a generic preference-based system for measuring comprehensive health status and health-related quality of life (HRQL). HUI® provides descriptive evidence on multiple dimensions of health status, a score for each dimension of health, and a HRQL score for overall health. Health dimensions include vision, hearing, speech, ambulation/mobility, pain, dexterity, self-care, emotion and cognition. Each dimension has 3-6 levels. The subjects will complete the HUI3[14, 15] at visit 1, 7 and 8.

7.3.10 The Abbreviated Profile of Hearing Aid Benefit (APHAB)

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The Abbreviated Profile of Hearing Aid Benefit (APHAB) [16]is a 24-item self-assessment, disability-based inventory that can be used to document the outcome of a hearing aid fitting, to compare several fittings, or to evaluate the same fitting over time. The subjects will complete the APHAB at visit 1, 7 and 8

7.3.11 Information recorded during surgery

The following information should be recorded during surgery:

- Type of surgery
- Skin thickness (skin thickness should not be measured in the control group since it is not in accordance with the surgical procedure when soft tissue reduction is performed)
- Length of the abutment
- Implant stability

7.3.12 Use of sound processor

The subjects will be asked at visit 6-10 how many days a week and hours per day they use the sound processor. Also the type of sound processor will be registered.

7.3.13 Implant Stability Quotient (ISQ)

ISQ will be measured at surgery as a baseline value and at visit 2-10.

The resonance frequency analysis renders an Implant Stability Quotient (ISQ) value ranging from 1 to 100. Measurements shall be performed at the abutment level. The highest and lowest ISQ value out of two perpendicular measurements obtained at each time point shall be recorded, ISQ High and ISQ Low.

The Osstell ISQ instrument and SmartPeg Type 55 (Osstell, Gothenburg, Sweden) shall be used. The procedure for obtaining ISQ values is described in the manufacturer's instruction.

7.3.14 Smoking habits

The subjects will at visits 1, 4, 6, 8, 9 and 10 complete a questionnaire regarding the use of nicotine:

	Subject response	
1	Does not smoke	
2	Less than 10 cigarettes/day	Low consumption
3	Between 11 and 20 cigarettes/day	Medium consumption
4	Between 21 and 40 cigarettes/day	High consumption
5	More than 40 cigarettes/day	Very high consumption

In Sweden a large proportion of adults use another form of tobacco, wet snuff. In the Swedish questionnaire the subjects will be asked if they use wet snuff and if so, the type of product and the quantity used per day.

7.4 Safety variables

7.4.1 Loss of implant

The loss of implant is defined as the actual loss of the implant from the site of implantation and will be recorded from visit 2 and onwards.

7.4.2 Device deficiency reporting

The definition of a device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

A device deficiency should be reported to the sponsor. A device deficiency that could have lead to a Serious Adverse Event (SAE) should be reported immediately (see next section).

7.4.3 Adverse Event (AE) and Serious Adverse Event (SAE)

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device

Serious Adverse Event (SAE)	Adverse event that a) led to death b) led to serious deterioration in the health of the subject, that either resulted in • a life-threatening illness or injury • a permanent impairment of a body structure or a body function • in-patient or prolonged hospitalization • medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment • to a body structure or a body function c) led to foetal distress, foetal death or a congenital abnormality or birth defect **Note** - Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event
Unanticipated Serious Adverse Device Effect USADE	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report

7.4.3.1 **Handling and reporting of AEs and ADEs**

Subjects will be carefully monitored during the investigation for possible adverse events and appropriate treatment of the subject will be initiated.

Any adverse events observed will be fully investigated by the investigator and documented in the case report form (CRF) including assessment of severity (mild, moderate or severe) and relationship to the medical device.

At visit 9 and 10 (week 101 and 156) only ADEs needs to be reported.

7.4.3.2 **Handling and reporting of SAEs and device deficiency that could have lead to a SAE**

An investigator should report within 24 hours, after being aware of the event, an SAE or a device deficiency that could have lead to a SAE. The report should be faxed or sent as a mail attachment to Cochlear Bone Anchored Solutions AB. Contact information is available on the SAE form.

7.4.4 Reporting to ethical committees and regulatory authorities

SAEs/SADEs/USADEs and device deficiencies that could have led to a SAE should be reported to ethics committees/institutional review board in accordance with local requirements.

7.5 Concomitant medication and treatments

All medications and treatments given, whether or not to treat AEs/ADEs, must be recorded in the appropriate section of the case report form.

8 Risk and benefits of the investigational device(s) and the clinical investigation

8.1 Anticipated clinical benefits

The Cochlear™ Baha® BA400 Abutment has been designed to remove the need to perform soft tissue reduction, to reduce skin complications and to improve the cosmetic outcome of the surgery. The surgical procedure will also be simplified.

8.2 Anticipated adverse device effects

The adjustment in the design of the new abutment is minimal from a risk perspective. Nevertheless the following risk with the new abutment BA400 in comparison with the current abutments BA300, has been hypothesised:

- Trauma
  A longer abutment (BA400: 10 mm and 12 mm abutments) could increase the risk for trauma in comparison with shorter abutments (BA300 6 mm/9 mm and Baha snap coupling 8.5 mm).

  In order to evaluate if longer abutments increase the risk of implant failure a comparison has been made between currently available abutments when it comes to reported implant failures in the Cochlear Complaint Management System (CREM) in relation to with the number of sold products.

  The conclusion of the events reported in CREM is that there is no indication of an increased risk of implant failures with the 9 mm abutment compared to the 6 mm abutment

Product	**Description**	**Number of sold products**	**Number of implant failures**
92127 BIA300	Implant 4 mm with abutment 6 mm	11 600	21
92346 BIA300	Implant 4 mm with abutment 9 mm	1 800	4

  A similar conclusion was drawn based on the literature search of Baha literature. Of the 55 articles selected for the clinical evaluation four (4) articles covered the use of the 8.5 mm long abutments. No implant failures were reported in these studies.

  In conclusion, there exist no anticipated additional adverse device effect in comparison with the current abutment (BA300).

8.3 Residual risks associated with the investigational device

Clinical outcomes related to the use of Baha implants and abutments have been frequently reported in the scientific literature during the last decades. A literature review[17] was performed in June 2012 in order to assess the current status of Baha implants and surgical products in terms of safety and efficacy. Fifty-five (55) scientific articles met the predefined review criteria. Only one (1) randomised controlled prospective study and one (1) non-randomised prospective study were encountered; the remaining studies were retrospective studies or case reports. One systematic literature review was also included. Ten (10) studies included only paediatric patients, while the remaining studies included

both paediatric and adult patients or adults only. Nineteen (19) of the studies included 100 or more patients.

Overall good outcomes, with acceptable implant survival rates and low incidence of significant adverse reactions, are reported. However, as with any surgical procedure, the use of Baha implants and surgical procedures is not free from complications, which is also reflected in the literature. Reported complications with Baha implants and surgical products are summarised at continuation.

Implant loss is a known complication with Baha implants, and can occur at any time point following implantation. Known reasons for implant loss include: primary failure of osseointegration, loss of osseointegration, trauma, infection leading to implant loss. The literature reports of cumulative implant survival rates in the range 73 to 100%, with the majority of authors reporting survival rates of 90% or higher.

Local skin reactions around the Baha abutment, ranging from slight redness to infected tissue, are the most common complications with Baha implants. Reports suggest that as many as 30% of the patients experience some kind of skin reaction at some point in time. However, the vast majority of skin complications are regarded as minor. Holgers grades of 0-1 are reported in 90-95% of observations, with adverse reactions (grade 2-4) only being reported in a few percent of observations

Excessive skin thickening or skin overgrowing the abutment is another relatively common soft tissue complication. The reported rate of skin thickening/overgrowth ranges between 0 and 22%. In cases where skin thickening recurs following localised treatment and skin revision surgery.

Incomplete or complete flap breakdown is another known complication with Baha implantation; this complication is generally not regarded as major.

Persistent pain at the implant site requiring removal of the implant has been reported by some author s and numbness in the area around the implant site has been reported in one study

8.4 Risks associated with participation in the clinical investigation

The test abutment, the control abutment and associated surgical procedures are CE marked and the procedures in this CIP are in accordance with the intended use.

8.5 Steps that will be taken to control or mitigate the risks

The surgical procedures associated with BA300 and BA400 are described in the Surgery Guides.

8.6 Risk-to-benefit assessment

After thorough analysis no foreseeable additional risks can be ascribed to the new abutment. Therefore the risks/adverse events are minimal and acceptable when weighed against the benefits of the intended performance of the investigational device/ comparator.

9 Statistical consideration

9.1 Statistical Design and Hypotheses considerations

9.1.1 Primary statsitical aims

This study 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 procedure and abutment BA300.

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.

9.1.2 Secondary statistical aims

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 infections/inflammations evaluated by Holgers Index
- reduction in soft Thickening/overgrowth scale
- reduction in time for wound healing will be 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

9.2 Sample size calculation

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

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

For a definition of first primary endpoint, see section 5.2.1. 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 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 we need 50 statistical evaluable subjects in each group. The sample size calculation is based on 10000 simulated studies.

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

For a definition of the second primary endpoint see section 5.2.1. 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 Hultcrantz[2] 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 costs time required for surgery,15% infections/inflammations, 15% extra dressings with skin reduction, 9% infections/inflammations and 10% extra dressings without skin reduction, w 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 need to randomize 53 subjects to each group

9.3 Analysis sets – populations

The Intention to Treat population (ITT) consists of all randomised patients with at least one follow-up measurement.

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.

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

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

9.4 General statistical methodology

For comparison between the two study groups the Mantel-Haenszel chi-square test will be used for ordered categorical variables, the Mann-Whitney U-test for continuous variables, Fisher's exact test for dichotomous variables and the Chi-square test for non-ordered categorical variables.

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

The main analyses will be performed on the ITT population and complementary analyses will be performed on the PP population.

The main analyses will be performed unadjusted. If significant statistical differences in demographics and baseline variables are found, complementary analyses will be performed adjusted for these variables.

The main analysis will be after 12 months of follow-up and repeated after 3 years.
All statistical tests will be two-sided.

9.5 Efficacy analysis

9.5.1 Primary efficacy analyses

9.5.1.1 First primary analysis: combined endpoint of infection/inflammation, overgrowth, pain and numbness

The primary analysis of the number of events regarding infection/inflammation, overgrowth, pain and numbness (see definition section 5.2.1) between the two study groups will be analysed with the Mantel-Haenszel two-sided chi-square test at a significance level of 0.0499 on the ITT population between 3 weeks and 1 year.

9.5.1.2 Secondary primary analyses: direct medical costs, based on time for surgical procedures, wound healing and complications

The primary analysis of direct medical costs, based on time for surgical procedures, wound healing and complications (see definition section 5.2.1) between the two study groups will be analysed with two-sided Mann-Whitney U-test at significance level 0.0001 on the ITT population up to one year of follow-up.

9.5.2 Secondary efficacy analysis

All secondary variables given in section 5.2.2 will be analysed and described with the methods given in section 9.4 General statistical methodology. All significance tests will be two-sided and conducted at the 5% significance level.

9.5.3 Tertiary efficacy analysis

All tertiary variables given in section 5.2.3 will be analysed and described with the methods given in section 9.4 General statistical methodology. All significance tests will be two-sided and conducted at the 5% significance level.

9.6 Safety analyses

The loss of implants will be analysed with the Log-rank test between the two groups and illustrated with Kaplan-Meier survival curves.

Adverse Events and Serious Adverse Events will be coded with the MedDRA dictionary and tabulated by PT-code and SOC-code and treatment.

9.7 Analyses of concomitant medications and treatments

Concomitant medications will be coded and tabulated by treatment.

9.8 Demographics and baseline characteristics.

Demographics and baseline characteristics are tabulated and analysed by treatment group according to the general methodology given in section 9.4.

9.9 Interim analysis

No interims analysis planned. In addition to the main analysis at one year, only a follow-up analysis after 3 years is planned.

9.10 Statistical Analysis Plan

A statistical analysis plan (SAP) with detailed statistical analyses specified for all variables and time points will be written and signed before the database lock.

10 Administrative part

10.1 Training

The Sponsor will organise an initiation visit during which the CIP, investigational procedures including the informed consent process, case report form completion and any other matters relating to running the investigation at the site should be discussed and queries clarified.

The principal investigator will ensure that appropriate training relevant to the investigation is given to the medical, nursing and other staff involved at the clinic and that new information of relevance to the performance of this investigation is forwarded to the staff involved.

10.2 Investigational data

10.2.1 Case report form

A paper document for each subject on which information that will be reported to the sponsor is recorded. Specific instructions how to complete the CRF will be provided to the investigator and other site staff. Completed CRFs will be reviewed and signed by an investigator.

10.2.2 Source data

Defined as all the information in original records, certified copies of original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation.

The CRF could be source data and before the initiation of the investigation the principal investigators should together with the monitor complete the template ‘Origin of source data’ stipulating where source data should be recorded at the investigational site.

10.2.3 Data management

A data management plan will be written that describes the overall data handling process including data validation, clarification of data and the clean file process.

All outstanding questions regarding data should be taken during the clean file meeting. After declaring clean file the data will be locked.

10.3 Archiving

The sponsor and principal investigator shall maintain the investigation documents as required by the applicable regulatory requirements.

10.4 Device accountability

Not applicable since the products are CE marked.

10.5 Quality control

10.5.1 Monitoring

The sponsor will appoint a monitor that will visit sites during the investigation. The monitor will be appropriately trained and informed about the nature of the investigation, ISO 14155:2011 and applicable regulatory requirements.

The monitor will verify the informed consent of participating subject, that the investigational team is adhering to the protocol and that data are accurately recorded in the CRF.

The monitor must have direct access to source data.

10.5.2 Audit

Audits of the clinical investigation may be conducted by the sponsor or third party designated by the sponsor to evaluate compliance with the CIP, written procedures, ISO-14155:2011 and applicable regulatory requirements.

10.6 Clinical Investigation Plan

10.6.1 Deviations from Clinical Investigation Plan

Any deviation from the CIP will be recorded together with an explanation of the deviation. Deviations will be reported to the sponsor, who is responsible for analysing them and assessing their significance. The appropriate ethics committee/institutional review board and regulatory authorities will be informed of any significant protocol deviations.

10.7 Suspension or premature termination

The sponsor may suspend or prematurely terminate either an individual investigation site or the entire clinical investigation for significant and documented reasons. A principal investigator may suspend or prematurely terminate participation in the clinical investigation at the investigation site for which he/she is responsible.

10.8 Publication policy

The result of this study will be published. Authors of the primary publication based on this study must fulfil the criteria defined by the International Committee of Medical Journal Editors (ICMJE).

The primary publication must be published before any secondary publications are submitted for publication.

10.9 Timetable

10.9.1 First subject in : Q4 2013

10.9.2 Last subject last visit: Q1 2017

10.9.3 Definition of end of investigation

End of investigation is defined as ‘last subject last visit.

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11 Signed agreement – sponsor

Title	**Clinical and health economic evaluation with a new Baha abutment design combined with a minimally invasive surgical technique** An international multicentre, open, randomised, comparative, parallel group, prospective clinical investigation. 1 year investigation with a 2 year follow-up
Investigation code	CBAS5439
Version	Final
Version date	19 SEP 2013

Signature of Cochlear Bone Anchored Solutions

I agree to the terms of this clinical investigation protocol, including all appendices.

Signature:

Mark Flynn
Director of Research and Applications

26 SEP 2013
Date (dd-MMM-yyyy)

43 (44)

12 Signed agreement – co-ordinating investigator

Title	**Clinical and health economic evaluation with a new Baha abutment design combined with a minimally invasive surgical technique** An international multicentre, open, randomised, comparative, parallel group, prospective clinical investigation. 1 year investigation with a 2 year follow-up
Investigation code	CBAS5439
Version	Final
Version date	19 SEP 2013

Signature of Co-ordinating investigator

I agree to the terms of this clinical investigation protocol, including all appendices.

Signature:

Signature:

Professor Robert Stokroos
Director of Research and Applications
Department of Otorhinolaryngology
Head and Neck Surgery
University Hospital Maastricht
Maastricht
The Netherlands

19 09 2013
Date (dd-MMM-yyyy)

44 (44)