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A clinical investigation of the benefit of directionality as a function of microphone location: BTE hearing aids versus ITE hearing aids.
Clinical Study Protocol

JUNE 22, 2018

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Clinical Study Protocol

Study Type:	Clinical trial with Investigational Medical Device (MD)
Study Categorisation:	Category C; medical device without CE Mark
Study Registration:	SNCTP, EudraCT
Study Identifier:	BF003-1808
Sponsor,	Bernafon AG Morgenstrasse 131, 3018 Bern
Principal Investigator:	Barbara Simon bsim@bernafon.com +41 31 998 16 84
Investigational Product:	Hearing Instrument; Mermaid 9
Protocol Version and Date:	Version 3.0, Final Document

Signature Page(s)

Study number	SNCTP; EudraCT, registration number (TBD)
Study Title	A clinical investigation of the benefit of directionality as a function of microphone location: BTE hearing aids versus ITE hearing aids.

The Sponsor, Investigator and trial statistician have approved the protocol version [3.0 (dated 22.06.2018)], and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm if applicable and the local legally applicable requirements.

Sponsor:

Printed name of Sponsor

Bruno Keller, Senior Director Marketing and Channel Support

Place/Date	Signature

Printed name of Principle Investigator: Barbara Simon

Place/Date	Signature

Printed name of Statistician: Christophe Lesimple

Place/Date	Signature

Printed name of Head of Regulatory Affairs: Asif Muhammad

Place/Date	Signature

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STUDY SYNOPSIS

Provide a structured synopsis containing all important information, preferably in tabular view:

Sponsor / Sponsor-Investigator	Bernafon AG
Study Title:	A clinical investigation of the benefit of directionality as a function of microphone location: BTE hearing aids versus ITE hearing aids
Short Title / Study ID:	BF003-1808
Protocol Version and Date:	2018.06.22; Version 3.0
Trial registration:	SNCTP, EudraCT
Study category and Rationale	Category C: Medical Device without CE mark
Clinical Phase:	Pre-market; Medical device validation study involving human subjects.
Background and Rationale:	The benefits of amplification and accessories used with it outweigh any risks in mild to profound hearing-impaired subjects. Hearing aids constantly undergo incremental improvements from already marketed devices. The new devices are expected to perform as well or better than the previous devices. Bernafon conducts clinical investigations to test whether the new technology provides the same or more benefit than previous Bernafon devices. Additionally, the aim of the testing is to grant quality control prior to product launch according to Bernafon development requirements. The current study will evaluate a new hearing aid hardware. The firmware driving the hearing aid has already been sold on the market using the Behind-the-Ear (BTE) hardware for almost one year and will now be launched using the In-the-Ear (ITE) custom hardware. The goal is to evaluate the audiological performance, usability, feature function, and to identify unexpected or unwanted behaviour from the devices. The study plans to compare the two hardware styles regarding the benefit received from different microphone locations. As human subjects are involved the validation falls under the definition of a clinical investigation. The validation will address the performance of the new chip using the ITE hardware, and ensure that there is no reduction in speech understanding between using the BTE and ITE hardware styles. Evaluating the overall performance of the Mermaid 9 ITE devices is important to validate that the end user is satisfied with the devices and that all user requirements are fulfilled. All features available in Mermaid 9 have been validated and are currently used on the market in Mermaid 9 BTE devices.
Objective(s):	The purpose of this study is to show that the performance of the ITE device is as good as the performance of the marketed BTE device. Furthermore, speech and comfort should not be negatively affected by the different hardware style. The usability of the devices, i.e. that the end users are able to handle the devices, should be as good as the marketed BTE device, and there should be no artefacts or unwanted noises.

Outcome(s):	Primary Endpoint: The primary objective is to assess the effect of microphone location on end users' speech scores. Two standardized speech tests will be used. The speech scores achieved with the IMD will be compared to those with the RMD. Secondary Endpoint: A secondary objective is to determine if the overall performance of the IMD is as good as the RMD. The performance of the IMD will be validated using a standardized questionnaire with the RMD as the control. The performance of the IMD should not be inferior to the RMD. Other/Safety Endpoint: The study aims to validate the overall implementation of the new chip with the ITE hardware. A product questionnaire will be used to report unexpected behavior from the IMD and find any new risk factors to ensure safety of the devices before they are released to the market.
Study design:	This is a controlled, open label, comparative clinical investigation conducted monocentric at the premises of Bernafon AG in Bern, Switzerland.
Inclusion / Exclusion criteria:	Inclusion Criteria: • All classifications of hearing loss (sensorineural, conductive, mixed) • If the hearing loss is conductive or mixed it must be approved for amplification by a physician • All shapes of hearing loss (flat, sloping, reverse slope, notch) • Severity ranging from mild to severe • German speaking • Current hearing aid users • Both genders • Ages 18 and older • Ability and willingness to sign the consent form Exclusion Criteria: • Contraindications for amplification • Active ear disease • Inability to follow the procedures of the study due to language problems, psychological disorders, dementia, or other cognitive problems of the participant • A reduced mobility making them unable to attend weekly study appointments • Uncooperative so that it is not possible to record a valid pure tone audiogram • A strongly reduced dexterity • Central hearing disorders • Bernafon employees • Family members of Bernafon employees

Measurements and procedures:	**Amplification** is verified and compared with targets using Real Ear Measurements **Speech intelligibility** is tested in background noise. Tests used include: Oldenburg Sentence Test (OLSA) and the Göttenburg Satztest (GÖSA). Speech tests are normally set up with speech in the front and noise at varying degrees around the participant. Tests such as the OLSA and GÖSA have a varying signal depending on the SNR goal. **Subjective perception of devices** is tested with questionnaires asking the participants various questions concerning the expectations and benefits of the hearing devices. They can be given independently for the two different devices and then compared against one another. **Preference testing** allows the participant to choose which hardware style that they prefer **Usability and handling** is measured with in-house questionnaires that target the new hardware and possible handling difficulties
Study Product / Intervention:	Mermaid 9 The new investigational medical device (IMD) will be the Mermaid 9 ITE hearing device. The Mermaid 9 BTE device is already CE marked and sold on the market for almost one year. The only difference between the devices is the hardware which results in a different location of the microphone (in the ear versus behind the ear). Hearing instruments are worn approximately 8-10 hours per day and removed at night. The test participants will wear the new devices for a time period of 10 +/- 7 days. They will have already been wearing BTE devices for at least 6 months. The IMD will be in a stable stage of development. This means that system testing will be complete to ensure correct implementation and safe behaviour of the devices before any testing on people is conducted. This also includes the software used to program the devices. The software will be at a stable stage of development.
Control Intervention (if applicable):	The reference devices are Mermaid 9 BTE hearing instruments.
Number of Participants with Rationale:	There will be an exploratory analysis of the data only. The total number of participants will be approximately 15-20.
Study Duration:	Approximately 1-2 months The screening of the participants will begin in May 2018 and the final data collection appointments will occur in July 2018.
Study Schedule:	The first participants will begin in June 2018 and the final data collection appointments will occur in July 2018.
Investigator(s):	Barbara Simon, Research Audiologist, Doctor of Audiology Morgenstrasse 131 3018 Bern, CH bsim@bernafon.com +41 31 998 16 84
Study Centre(s):	The testing will be performed at a single site in Bern, Switzerland at the Bernafon AG headquarters.
Statistical Considerations:	The analysis and documentation will be performed by the statistician using the latest validated R version with R Studio as IDE. Appropriate data analysis will be performed with parametric and non-parametric tests on questionnaire outcomes, hearing threshold measures, and speech test scores.
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP or ISO EN 14155 (as far as applicable) as well as all national legal and regulatory requirements.

ABBREVIATIONS

Provide a list of abbreviations used on the protocol - to be completed

AE	Adverse Event
BASEC	Business Administration System for Ethical Committees, (https://submissions.swissethics.ch/en/)
CA	Competent Authority (e.g. Swissmedic)
CEC	Competent Ethics Committee
CRF	Case Report Form
ClinO	Ordinance on Clinical Trials in Human Research *(in German: KlinV, in French: OClin, in Italian: OSRUm)*
eCRF	Electronic Case Report Form
CTCAE	Common terminology criteria for adverse events
DSUR	Development safety update report
GCP	Good Clinical Practice
IB	Investigator's Brochure
Ho	Null hypothesis
H1	Alternative hypothesis
HRA	Federal Act on Research involving Human Beings *(in German: HFG, in French: LRH, in Italian: LRUm)*
IMP	Investigational Medicinal Product
IIT	Investigator-initiated Trial
ISO	International Organisation for Standardisation
ITT	Intention to treat
MD	Medical Device
MedDO	Medical Device Ordinance *(in German: MepV, in French: ODim)*
PI	Principal Investigator
SDV	Source Data Verification
SOP	Standard Operating Procedure
SPC	Summary of product characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File

STUDY SCHEDULE

Study Periods	Intervention Period		
Visit	Screening/1	2	3
Day	0	10 +/- 7 days	20 +/- 5 days
Patient Information and Consent	x		
Demographics	x		
Medical/Hearing History	x		
In-/Exclusion Criteria	x		
Randomization		x	x
Otoscopy	x	x	x
Audiometry	x		
Ear Impressions	x		
Administer Medical Device	x	x	
Primary Variable (speech testing)		x*	x*
Secondary Variables (APHAB)	x	x	
Secondary Variables (product questionnaire)	x	x	
Other Variables (preference questionnaire)			x
Adverse Events	x	x	x

*Randomization of lab trial test conditions

1. STUDY ADMINISTRATIVE STRUCTURE

1.1 Sponsor, Sponsor-Investigator

Bernafon AG

Morgenstrasse 131, 3018 Bern

Tel. +41 31 998 01 01

The role of the sponsor is to provide the site for the testing as well as the equipment used during testing. The sponsor will provide the hearing devices, the IMD, and the RMD used for the study. The results will be used by the sponsor to prove the performance of the IMD. The sponsor may audit the clinic as well as the processes and documentation performed by the investigators at that site.

1.2 Principal Investigator(s)

Barbara Simon, Research Audiologist

Morgenstrasse 131, 3018 Bern

Tel. +41 31 998 16 46

Email: bsim@bernafon.com

1.3 Statistician ("Biostatistician")

Christophe Lesimple

Morgenstrasse 131, 3018 Bern

Tel. +41 31 998 17 03

Email: cles@bernafon.com

1.4 Laboratory

Not applicable

1.5 Monitoring institution

Bernafon uses monitoring to oversee the study and verify that the conduct of the clinical investigation complies with the approved CIP, subsequent amendment(s), ISO14155, and the applicable regulatory requirement(s). There will be a specific person assigned as the Monitor (sec. 1.7).

1.6 Data Safety Monitoring Committee

There will not be a data safety monitoring committee employed. The data will be stored using an accepted and validated data storage management system.

1.7 Any other relevant Committee, Person, Organisation, Institution

Julie Tantau will monitor the investigation. She works within the Product Validation group at Bernafon. She is certified in GCP, and familiar with ISO 14155. She has also been certified in Clinical Monitoring and has a CAS I in Clinical Trial Practice and Management.

2. ETHICAL AND REGULATORY ASPECTS

Before the study will be conducted, the protocol, the proposed patient information and consent form as well as other study-specific documents shall be submitted to a properly constituted Competent Ethics Committee (CEC) and Swissmedic. Any amendment to the protocol must as well be approved (if legally required) by these institutions.

The decision of the CEC and Swissmedic concerning the conduct of the study will be made in writing to the Sponsor before commencement of this study. The clinical study can only begin once approval from all required authorities has been received. Any additional requirements imposed by the authorities shall be implemented.

2.1 Study registration

The study shall be registered in the EU registry of clinical trials, EudraCT (https://eudract.ema.europa.eu/eudract-web/index.faces). Additionally, the study will be registered in German in the Swiss national clinical trials portal (SNCTP).

2.2 Categorisation of study

The clinical trial of these medical devices falls under Category C because the hearing aids will not yet have the conformity marking at the time of the trial. The IMD is equivalent in all except hardware to the RMD with CE Declaration of Conformity and will be used with the same intended purposes as those with the conformity marking.

Use of the devices is not prohibited in Switzerland.

2.3 Competent Ethics Committee (CEC)

The responsible investigator ensures that approval from an appropriately constituted Competent Ethics Committee (CEC) is sought for the clinical study.

The responsible investigator will report any changes as well at the end of study within the allowed time frame (including changes to the research activity and all unanticipated problems involving risks to humans; including in case of planned or premature study end and the final report). No changes will be made to the protocol without prior Sponsor and CEC approval, except where necessary to eliminate apparent immediate hazards to study participants.

Premature study end or interruption of the study is reported within 15 days. The regular end of the study is reported to the CEC within 90 days, the final study report shall be submitted within one year after study end. Amendments are reported according to chapter 2.10.

2.4 Competent Authorities (CA)

The Sponsor will obtain approval from Swissmedic before the start of the clinical trial. CA approval is necessary for all studies of category C (MD).

The Sponsor will report any changes as well as the end of study within the allowed time frame (including changes to the research activity and all unanticipated problems involving risks to humans, including in case of planned or premature study end and the final report). No changes will be made to the protocol without prior Swissmedic approval, except where necessary to eliminate apparent immediate hazards to study participants.

Premature study end or interruption of the study is reported to the CA and Swissmedic within 15 days. The regular end of the study is reported to the CA within 90 days, the final study report shall be submitted within one year after study end. Amendments are reported according to chapter 2.10.

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2.5 Ethical Conduct of the Study

The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH, in case of medical device: the European Directive on medical devices 93/42/EEC and the ISO Norm 14155 and ISO 14971, the Swiss Law and Swiss regulatory authority's requirements. The CEC and regulatory authorities will receive annual safety and interim reports and be informed about study stop/end in agreement with local requirements.

2.6 Declaration of interest

It is the policy of Bernafon AG that the conduct of employees and all other persons acting as its representatives should be always in the best interests of Bernafon AG, its members and the public. In performing their duties, Bernafon AG representatives should not be influenced by desire for personal gain. Accordingly, Bernafon AG has adopted rules to guide disclosure of potential conflicts of interest and the society's response thereto that shall apply to those who agree to serve Bernafon AG in any official capacity.

2.7 Patient Information and Informed Consent

The participants will be informed about the study by the PI or other investigator during the first visit. The explanation will include what type of testing will be involved, how long it will last, and who will do the testing. Consent is sought from each participant. They will be compensated with hearing aid accessories (i.e. Batteries, cleaning supplies) that will not exceed a value of 100 CHF.

The investigator will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant will be informed that the participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment.

The participant must be informed that his/her medical records may be examined by authorized individuals other than their treating physician.

All participants for the study will be provided a participant information sheet and a consent form describing the study and providing sufficient information for participant to make an informed decision about their participation in the study. Enough time needs to be given to the participant to decide whether to participate or not. If they require more than the 1.5 hours allotted for the appointment they can take the information home and have 24 hours in which to decide.

Otherwise, the participants will sign the consent form in the clinic during the first visit if they choose to become a participant.

The patient information sheet and the consent form will be submitted to the CEC to be reviewed and approved. The formal consent of a participant, using the approved consent form, must be obtained before the participant is submitted to any study procedure.

The participant should read and consider the statement before signing and dating the informed consent form, and should be given a copy of the signed document. The consent form must also be signed and dated by the investigator (or her designee) and it will be retained as part of the study records.

The formal consent of a participant, using the approved consent form, must be obtained before the participant is submitted to any study procedure.

2.8 Participant privacy and confidentiality

The investigator will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspections

and will provide direct access to source data and/or documents.

Additionally, the investigator affirms and upholds the principle of the participant's right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilising subject identification code numbers to correspond to treatment data in the computer files.

The subject identification numbers have no relation to any subject private data (e.g. Birthdate). The numbers are assigned as the subjects join the subject pool. The number and corresponding subject name are written in a document that is stored in a secured document management system. The document can be opened with a security access code of 11 characters that is only given to study personnel that work with subjects (e.g. investigators/ audiologists).

For data verification purposes, authorized representatives of the Sponsor (-Investigator), Swissmedic, or an ethics committee may require direct access to parts of the medical records relevant to the study, including participants' medical history.

2.9 Early termination of the study

The Sponsor and/or CEC and/or Swissmedic may terminate the study prematurely according to certain circumstances for example:

- ethical concerns,
- insufficient participant recruitment,
- when the safety of the participants is doubtful or at risk, respectively,
- alterations in accepted clinical practice that make the continuation of a clinical trial unwise,
- early evidence of benefit or harm of the experimental intervention

2.10 Protocol amendments

The PI is allowed to amend the protocol or to provide suggestions for a protocol amendment. Any plans for protocol modifications will first be approved by the relevant parties (including, other investigators, CEC, and Swissmedic) before amending the protocol.

Substantial amendments are only implemented after approval of the CEC and CA respectively.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the CEC/CA. Such deviations shall be documented and reported to the sponsor and the CEC/CA as soon as possible.

All non-substantial amendments are communicated to the Swissmedic as soon as possible if applicable and to the CEC within the Annual Safety Report (ASR).

3. BACKGROUND AND RATIONALE

3.1 Background and Rationale

According the World Health Organization (WHO, 2016) 360 million people worldwide suffer from disabling hearing loss. Hearing aid amplification is the most common treatment for hearing loss. Benefits of amplification and accessories used with it outweigh any risks in mild to profound hearing-impaired subjects. A clinical literature evaluation is maintained and updated by Bernafon for new products. The evaluation concludes that, “Hearing device use is “a non-invasive, comparatively low risk option with considerable potential benefits”. As presented in the general literature evaluation, substantial scientific clinical literature shows that amplification of sound provides the claimed benefit for hearing impaired persons. The literature shows both significant improvements in speech intelligibility and improved life quality (Kochkin, 2011). The benefits are obtainable for both unilateral and bilateral fittings and are both short term and durable on long term.

In May of 2017 Bernafon released a new hearing aid on the market with an upgraded chip capable of more memory and faster processing. This release only included behind-the-ear styles of hearing aids, and they will now release the custom in-the-ear styles to complete the portfolio. There are generally no differences in the overall benefit that each style provides. However, the difference in microphone location of each style does inherently contribute to small differences in localization and directionality benefits. The effects of other features such as noise reduction can also be affected by the microphone location. The style is normally determined based on hearing loss, personal preferences of the end user, and potential handling difficulties. The hearing loss is a factor because an ITE fills the entire ear canal which can cause occlusion. A person with normal to mild hearing loss in the low frequencies will find it more difficult to hear with an ITE because it will block already audible sound from entering the ear canal whereas, an open fit BTE will allow these sounds to naturally enter the canal without amplification. However, for those with severe to profound hearing loss an ITE may not provide sufficient power so a BTE is required in order for them to receive the correct amount of amplification. Those with handling difficulties may find an ITE easier to manipulate. Bernafon has sold ITE hearing aids on the market since the 1970’s, but they will now introduce the style with the updated processing chip.

For this study, Bernafon AG will carry out testing with participants who have hearing loss to validate the performance and qualify the benefit for the user with the ITE style of hearing aids and the new chip. Studies have investigated the differences between open and closed fittings and found that when using directional microphones, the closed fitting provided a greater speech intelligibility benefit between 1.6 and 3 dB compared to the open fittings (Winkler et al., 2016).

For the current study, the ITE hearing aid is the IMD, and the BTE style that is currently sold on the market will be the RMD and comparator. The results of the trial will be used to examine differences in benefit provided between the styles as well as identify further optimization of the tested products. The hearing aids will be programmed with the prescribed gain and features. The aim is to determine whether there is a difference in the benefit provided by each style. Objective measures of the output of both styles will be made with Real Ear Measures (REM) and speech tests, and subjective differences will be measured with questionnaires. The prescribed gain could be adjusted depending on the REM output in order to provide a similar target match between the RMD and IMD.

All participants are hearing impaired persons that have been wearing BTE hearing aids for at least 6 months. They will be fit with the RMD and the IMD during the trial. There are only small potential differences expected due to the different microphone locations of the custom hardware style. Therefore, the IMD should perform as well as the RMD.

In summary, the primary reason for this study is to evaluate the new hearing aid hardware style with the upgraded chip. The goal is to evaluate the audiological performance, possible microphone location effect, and safety of the new hearing aids before they’re released to the market.

3.2 Investigational Product (treatment, device) and Indication

The investigational product (IMD) is a class IIa medical device. The brand name is Mermaid 9, manufactured by Bernafon AG. The software version used to program the devices is Oasis^{nxt}. The device is intended for people with hearing loss over 36 months of age. They are equivalent to those

with CE Declaration of Conformity; however, do not have the physical marking on them yet. The device consists of a body made of plastic that houses the speaker, microphone(s), and chip. Only the plastic is in contact with the skin of the inside of the ear canal. Only those trained as a hearing care professional in the fitting of hearing devices should program the device. However, anyone who receives a minimum amount of explanation concerning the use of the device is qualified to use it. The device is non-invasive and requires no surgical procedures.

3.3 Preclinical Evidence

Bernafon requires evidence of operational safety and medical effectiveness of the devices before testing them. This evidence includes the device-related performance data in accordance with IEC 118-7: Measurement of the maximum output level and the maximum gain. In addition to the performance testing, the hearing aids are verified with system tests to ensure that they function according to the requirements. The safety of the fitting software is demonstrated by a beta version that has passed through a complete systematic software test and ensures the functionality of the hearing aids in combination with the software. Please see chapter B3e of the IB.

3.4 Clinical Evidence to Date

A clinical literature evaluation is maintained and has been updated in 2017. The basic benefit of hearing aids does not change with newly released devices. They are designed to amplify sound. The benefit of hearing aids has been shown in various studies (Kochkin, 2011). The evaluation includes an analysis of adverse events for Bernafon products as well as competitor devices that is used as post market analysis of the devices. The same Mermaid 9 device in a different hardware style was released to the market in early 2017. To date, there have been no adverse events reported on the U.S Food and Drug (FDA) Manufacturer and User Facility Device Experience (MAUDE) website.

Studies have concluded that different hearing aid styles can have an influence on comfort, occlusion, and feature functionality (Winkler et al., 2016). However, they all still provide the benefit of amplification.

A risk assessment is performed for all new devices. The primary risk identified is the possibility of over amplification from excessive sound pressure levels (further described in sec. 3.7). This risk is mediated by printing a warning in the Instructions for Use for hearing aids with high sound pressure level output capability. Additionally, when this type of instrument is selected in the software, there is a message warning the HCP of the sound pressure capability. Overall, Bernafon AG has had no adverse event reported in the last 16 years including no required modifications or recalls of products.

3.5 Medical Device: Rationale for the intended purpose in study (pre-market MD)

The IMD will be used in accordance with current use of hearing devices. The intended purpose of the study is to compare the performance of the IMD with the RMD that is currently sold on the market. In order to make an effective comparison the test participants will wear the IMDs for approximately 2 weeks.

3.6 Explanation for choice of comparator

The comparison device will be the current equivalent Bernafon BTE style of hearing aid (RMD) that has been available on the market since early 2017. The test participants will be fit with these devices during the trial to be able to compare them to the IMD. The reason for using the RMD is to control for performance differences caused by the new ITE style. Using a different style should, in theory, not affect the performance of the device.

3.7 Risks / Benefits

The audiological and psychoacoustic investigations are conducted using volunteer test participants with sound pressure levels that will not endanger their residual hearing. The test participants will be advised of the type, content, extent, and possible risks of the test beforehand. As psychometric methods are involved in the data collection, the risk for the test participants is judged to be extremely minor. However, the following risks shall be addressed:

Risk of hearing loss to residual hearing at too high a level in audiological and psychoacoustic experiments: Due to the test design (use of noise level up to a maximum of 100 dB SPL) and the hardware limitations of the measuring equipment (maximum output of loud speaker) the maximum provided sound level is restricted. During audiometry (test of hearing loss with audiometer) a level of more than 100 dB SPL must be used for test subjects who are profoundly hard of hearing; however, test subjects with profound hearing loss are not part of the inclusion criteria for this study

Post-trial care is organized in a manner that allows the test participants to contact the sponsor site and arrange an appointment for any maintenance of the devices as needed.

A device risk analysis and risk assessment have been conducted for the new device according to EN ISO 14971. This describes the anticipated adverse device effects, residual risks associated with the investigational device and the procedures involved in its use. It also explains that the anticipated clinical benefit outweighs the potential risks. Please see the Risk Assessment for details.

3.8 Justification of choice of study population

The choice of study population was determined by the goal of the study. The intended purpose of the study is to compare current Bernafon device performance against the new device and not the overall effect of amplification. Therefore, only participants that are hearing impaired and experienced hearing aid users will be included. Bernafon has its own database of test subjects that are used for clinical trials. They are current hearing aid users that use the Bernafon clinic for adjustments to fittings and general maintenance of their hearing aids performed by the audiologists working at Bernafon. These test subjects do not consist of employees of Bernafon or family members of employees. The test subjects for the current study will be chosen from this internal subject database.

The comparison between devices shall be made with experienced hearing aid users. It is important to compare the performance of the devices and the subjective opinions of the intended users. Testing normal hearing participants would not contribute information to this study. Test participants must be able to sign and understand the consent form to be included in the study. For emergency situations, the following applies:

-The standard procedure is to recommend that a subject see the ENT with whom they have an established relationship. If a subject does not have an ENT then it is agreed with Dr. Carvacchio (Inselspital, Bern) that, if necessary, subjects from the trial could be referred to him.

4. STUDY OBJECTIVES

4.1 Overall Objective

The purpose of this study is to evaluate whether the IMD provides a similar or better performance than the RMD. The study aims to provide a final validation and quality control of the IMD before it is released for sales.

4.2 Primary Objective

The primary objective is to assess the effect that microphone location has on the speech scores of the end users. The speech scores of the IMD will be compared to the RMD.

4.3 Secondary Objectives

A secondary objective is to determine if the performance of the IMD is as good as the RMD. The performance of the IMD will be validated using the RMD as the control. The performance of the IMD should not be inferior to the RMD. The performance will be measured for both the RMD and IMD using a standardized questionnaire.

4.4 Safety Objectives

The study aims to validate the overall implementation of the new chip with the ITE hardware. The study will test for unexpected behavior from the IMD and new risk factors to ensure safety of the devices before they are released to the market. A product questionnaire will be used to evaluate safety factors.

5. STUDY OUTCOMES

5.1 Primary Outcome

The primary outcome variable will be the speech scores measured with two speech tests and in three conditions: unaided, with the control (RMD), and with the new device (IMD). Speech scores should be equal to or better than those achieved with the RMD. A non-inferiority test will measure whether the location of the IMD microphones provide as good as or better speech scores than the location of the RMD microphones with a reference speech test. The second test uses different speech material to measure the microphone location effect and should generalize the results to wider listening conditions. The unaided condition will be used as a control of the IMD benefit if superiority cannot be shown.

5.2 Secondary Outcomes

The secondary outcome will be measured with questionnaires. A standardized questionnaire and two in-house questionnaires that ask questions specific to the study objectives will be completed by the test subjects. The standardized questionnaire provides a standard scoring method for comparing the overall performance of the two devices, and the in-house questionnaires will specifically address localization, comfort, and occlusion factors between the devices, as well as preference for the two styles.

5.3 Safety Outcomes

The in-house questionnaire will also ask questions regarding the safety of the devices to address the occurrence of unexpected noise or behavior from the devices. Unexpected behavior includes unprovoked feedback or whistling, distorted sounds or artefacts, discomfort, spontaneous muting or shutting off, unexplained warning signals or beeps, and louds sounds. The information provided from the field trial will alert the Sponsor to potential safety risks that should be addressed before releasing the device to the market.

6. STUDY DESIGN

6.1 General study design and justification of design

This is a controlled, randomized, open label, comparative clinical investigation conducted monocentric at the premises of Bernafon in Bern, Switzerland.

The exploratory study is based on a population of approximately 20 hearing impaired people that have a hearing loss appropriate for the IMD.

As an RMD, the subjects will be fit with Mermaid 9 BTEs during the trial. Additionally, a control situation will be the unaided test condition for speech testing.

There is no placebo or device that does not provide amplification. A single group assignment design is used with test subjects that have worn BTEs for approximately 6 months and will be fit with the RMD and IMD during the trial. The testing is unblinded as the main difference between the IMD and the RMD is hardware and therefore obvious to the end user that it's different.

A randomized test order will be used to test in a simulated environment. The test subjects will be tested using unaided and two aided conditions in a randomized manner for speech testing.

The participants are expected to participate for approximately 2-3 weeks for a combination of field and lab tests. There are two lab tests planned during which the participants will not spend more than 2 hours in the clinic (including breaks). The field test periods will not last more than 10 +/- 7 days.

The sequence will begin with the screening appointment in which participants are invited to the clinic for testing to determine if they are candidates for the trial. The entire test procedure will be explained, and they will be given a Patient Information and Informed Consent which will need to be signed, dated, and returned before any testing begins. If they choose to participate, a hearing test will be made to determine if they have an appropriate hearing loss, ear impressions will be made to make the custom fitting IMD, and the RMD will be fitted

The following appointments will include fitting of the IMD, field tests during which they will wear the RMD and IMD, and lab tests in the clinic. There will be a total of 3 appointments , and each appointment will not exceed 2 hours. During the lab tests in the clinic they will participate in speech testing. Test subjects will be given questionnaires to complete at home and in the clinic.

After they have completed all appointments, the subjects will receive instructions about the continued use of their own hearing aids, and the reminder that they are welcome to come to the clinic for any maintenance or other follow-up of the hearing aids.

6.2 Methods of minimising bias

6.2.1 Randomisation

A single group assignment to the IMD will be used. The test order will be randomized based on list created by the statistician. This means that for the speech tests the subjects will be randomized by the condition. This reduces bias by using a different starting and ending condition as the last condition has a higher chance of scoring higher due to a learning effect from the speech test. The list will not be concealed, but should be in the ISF so that the PI knows in which condition order to test each subject.

6.2.2 Blinding procedures

The testing will be unblinded as the differences in the hardware of the device make it impossible to blind.

6.2.3 Other methods of minimising bias

A validated questionnaire to compare the overall performance between the IMD and RMD will be used to minimize bias. Additionally, the RMD will be programmed to a standard first fit setting that will be consistent with the electroacoustic fitting of the IMD. The RMD will be fit at the first appointment when the ear impressions are made for the IMD. They will wear the RMD for approximately 10 +/- 7 days with the standard fitting before returning to the clinic for the IMD fitting. The equivalent fitting will reduce bias that subjects may otherwise have toward their previous BTE fitting.

6.3 Unblinding Procedures (Code break)

N/A, the study is performed unblinded.

7. STUDY POPULATION

The study will take place in the clinic at Bernafon AG in Bern. No other sites will be used for the testing.

7.1 Eligibility criteria

Participants fulfilling all of the following inclusion criteria are eligible for the study:

- All classifications of hearing loss (sensorineural, conductive, mixed)
- If the hearing loss is conductive or mixed, it must be approved for amplification by a physician
- All shapes of hearing loss (flat, sloping, reverse slope, notch)
- Hearing loss severity ranging from mild to severe
- German speaking
- Both genders
- Ages 18 and older
- Ability and willingness to sign the consent form
- Current BTE hearing aid user

The presence of any one of the following exclusion criteria will lead to exclusion of the participant:

- Contraindications for amplification
- Active ear disease
- Inability to follow the procedures of the study due to language problems, psychological disorders, dementia, or other cognitive problems
- A reduced mobility making them unable to attend weekly study appointments
- A reduced ability to describe auditory impressions and the usage of the hearing aids
- Uncooperative so that it is not possible to record a valid pure tone audiogram
- A strongly reduced dexterity
- Central hearing disorders
- Bernafon employees
- Family members of Bernafon employees

7.2 Recruitment and screening

Bernafon has its own database of test subjects that use the Bernafon clinic for updated fittings and general maintenance of their hearing aids. These test subjects do not consist of employees of Bernafon or family members of employees. The test subjects for the current study will be chosen from the internal subject database. Bernafon does not advertise as a method of recruiting participants. Participants are collected and added to the database by word of mouth. If a current person from the database knows of another person with hearing loss they may give them the contact information of an audiologist within Bernafon. The person can then contact Bernafon if they wish to have a hearing test and determine if they're eligible to participate in a study. They are given a diagnostic audiological exam to determine if they have a hearing loss and the severity. If there are any medical indications it is recommended that they see a physician and then return if there are no contra-indications for hearing aids. During the hearing exam and medical history discussion it is determined whether the person is cognitively able to act on their own behalf. Additionally, if the person comes alone or if they are accompanied will help to determine their level of independence. If there is a study that is ready to take place then that will be explained at this time including an estimation of how much time/number of appointments would be required of them. If there is no immediate study planned, the normal study process will be explained to the subjects and they will be put on a waiting list. It is explained that the general compensation for their time is by means of a box of batteries and cleaning accessories.

7.3 Assignment to study groups

For the field tests the allocation is single group; therefore, all the test subjects will be assigned to the same group. The initial field test will be with the RMD and the second with the IMD, as it will take time

to have the IMD made by the lab.

For the lab tests the assignment to the test condition order will be randomized by the statistician. The test condition order will be randomized using a latin square design. This will minimize bias created when one test condition is tested in the final or last position all the time.

7.4 Criteria for withdrawal / discontinuation of participants

Participants are allowed to withdraw from the study at any time and for any reason. They do not have to share the reasons with the investigator. They will be asked to return the IMD. If the decision to withdraw is made by the investigator, the PI will inform the subject in person that they are no longer needed for the study. Reasons for withdrawing a participant from the study could be for non-compliance during testing, unreliable responses, medical reasons such as an ear infection, or the study may need to be stopped or postponed. Any data gathered from these subjects will be used for the current study. All data will remain encoded because results are only recorded using the identification code of the subject. There are normally at least five “back-up” test participants on the list to replace those that withdraw or are withdrawn. The “back-up” participants have already been screened and deemed to be appropriate for the study.

8. STUDY INTERVENTION

8.1 Identity of Investigational Products (medical device)

The treatment will be approximately 2 weeks of use with the IMD during which they will not use the RMD. During the study they will stop using the RMD and switch to the IMD for the assigned period.

There will be lab tests during which the participants will use the RMD and the IMD, for up to 2 hours at a time during testing in the clinic.

8.1.1 Experimental Intervention (medical device)

The investigation product (IMD) is a medical device. It is a new version of a Bernafon hearing device. The name is Mermaid 9 ITE. The Mermaid 9 BTE style was released to the market in early 2017. The Mermaid 9 ITE does not deviate from the current commercial product except for the hardware style. The ITE is fitted completely in the ear canal and concha of the ear while the BTE style fits with the body of the device over the ear, and a dome or earmold inside of the ear canal. Performance of the IMD is expected to be the same as the RMD. They are non-invasive devices. The hearing aid is worn inside the ear canal and is made from non-toxic plastic with an acrylic coating. A comparison of the hardware styles is shown in Figure 1.

Figure 1. Mermaid 9 ITEs (left) and Mermaid 9 BTEs (right).

8.1.2 Control Intervention (comparator medical device)

The Reference Medical Device (RMD) is the Mermaid 9 BTE as shown above in Figure 1. It is a CE marked hearing aid that was released to the market in 2017. The intended purpose of both devices is the same-to amplify sounds. The strength of the amplification is programmed according to the subject's individual hearing loss. There is no placebo treatment used as the study uses the accepted standard treatment for hearing loss as the control. The RMD and the IMD will be programmed based on each participant's hearing loss. The amplification will be set for both devices as determined using the REM data. The output amplification will be tested for both the RMD and the IMD to ensure that they are similar.

8.1.3 Packaging, Labelling and Supply (re-supply)

The IMD is labelled by printing the name of the device directly onto the device. There is an individual serial number that also printed on the device. The production batch can be tracked through this serial number. The hearing aids are shipped in a box with a label on the outside of the box that states the name of the product, the serial number, and a short description. Inside the box is a case that houses the hearing aids. The HCP removes the case from the box, and the case is generally given to the end user in which to place the hearing aids whenever they are not worn. The packaging and labelling are the same for the IMD and the RMD.

8.1.4 Storage Conditions

The IMD devices are shipped as soon as they are produced because they are custom devices which are made to order. Therefore, they are not stored on any shelves. The conditions in which they should be shipped and kept by the end user are described in the IFU. They should not be exposed to temperatures below -25° and not above 60° Celsius.

8.2 Administration of experimental and control interventions

8.2.1 Experimental Intervention

The IMD is worn completely inside the ear canal. It is non-invasive. The amplification is prescribed based on the participant's hearing loss. The IMD will be worn by each participant for approximately 2 weeks to give the subjects enough time to wear the devices in different environments and make a comparison between the IMD and the RMD. Normal use of a hearing aid is 8-10 hours per day. The participants will wear the IMD for the same amount of time during the day that they wear the RMD. The hours of daily use will be controlled with a data logging feature in the software that programs the hearing aids.

The study procedure will use a single group assignment design in which the subjects will wear the IMD at the same time. As stated previously, the device is non-invasive and requires no surgical procedure. The device is inserted into the ear canal where it fits the subject's ear canal only as they are custom instruments and made from an impression of the subject's ear canal.

8.2.2 Control Intervention

The RMD is worn over the ear with a piece (earmold or dome) that is worn inside the ear canal. The RMD is the current marketed device. They will use the RMD programmed for the current study for approximately 10 +/- 7 days and then switch to the IMD. They will compare the IMD to the RMD after the 10-day field test with the IMD. Normal use of a hearing device is 8-10 hours per day. They will wear the RMD and the IMD for the same amount of time each day. The hours of daily use will be controlled with a data logging feature in the software that programs the hearing aids.

The study procedure will use a single group assignment design. The subjects will have already worn the RMD during the first period, and will then all wear the IMD at the same time during the second period. As stated previously, the device is non-invasive and requires no surgical procedure. The RMD device is placed over the ear and the dome or earmold is placed inside the ear canal. The subjects themselves will place the device in their ears each morning and remove them each night for sleeping. The test subjects are experienced users of the BTEs, same style as the RMD, and will have been placing it on their ears for at least 6 months before beginning the current study. They will have been given an Instructions for Use booklet when fitted with the devices that explains how to insert the device and provides further instructions concerning cleaning, battery changing, and warnings.

8.3 Device modifications

The IMD will provide the similar amplification as the RMD; therefore, the subject should not experience any significant negative differences that would make the subjects want to discontinue use of the device. However, if a subject does report such differences, that can be improved with fine tuning, fine tuning can be made to improve the situation enough for the subject to continue with the study. If the subject requests to discontinue they can immediately remove the IMD from their ear and return to using their own BTEs. They will be asked to return the IMD to Bernafon AG, but their data will still be included in the results for the current study. All data will remain encoded because the results are only recorded using the identification code of the subject.

8.4 Compliance with study intervention

It is clearly explained to the subjects that during the period of intervention it is important to the study that they only wear the RMD and IMD. However, their own BTEs are left in their possession for safety reasons in the event that they choose to discontinue their participation in the trial or a problem arises with the test devices. For ethical purposes, the subjects must have a back-up solution for their hearing impairment.

The data logging feature of the software monitors the average number of hours that the devices are worn each day. Therefore, it will be noted if the RMD and IMD have not been worn a standard or expected amount of time.

8.5 Data Collection and Follow-up for withdrawn participants

Any data that is collected will be kept in the data management database. The data will remain encoded because results are only recorded using the identification code of the subject. The analysis and report will include a section based on the data available from all recruited subjects (as the intention to treat ITT) and another section based on the data from the subjects that complete the entire protocol (per protocol PP). Withdrawn subjects will have the same follow-up as those subjects that complete the trial. As all subjects are taken from the Bernafon database, all participants, including those that withdraw, are welcome to return to the clinic for fine-tuning and maintenance as needed.

8.6 Trial specific preventive measures

The performance of a hearing aid is not impacted by medication. The subjects will continue to take whatever type of medication that they normally take. There will be no impact on the study objectives.

8.7 Concomitant Interventions (treatments)

Test subjects will continue to receive any concomitant care and medication that they normally receive during the trial. All test subjects will already be hearing aid users and will have, therefore, used them while receiving other types of care or medications. There will be no impact on the study objectives.

8.8 Medical Device Accountability

The RMD and IMD devices have serial numbers by which the individual device can be identified and the production history traced. The devices will be shipped from the production lab in Poland. The serial numbers will provide traceability of their production. All devices undergo testing in production before being shipped. Only IMD that are from a tested batch will be used in the study.

8.9 Return or Destruction of Medical Device

At the end of the study all of the subjects will return the IMD to the site in Bern. It will be noted in the device accountability log and CRF that the devices were returned.

The PI will then return the devices to the Sponsor.

9. STUDY ASSESSMENTS

9.1 Study flow table of study procedures and assessments

Study Periods	Intervention Period		
Visit	Screening/1	2	3
Day	0	10 +/- 7 days	20 +/- 5 days
Patient Information and Consent	x		
Demographics	x		
Medical/Hearing History	x		
In-/Exclusion Criteria	x		
Randomization		x	x
Otoscopy	x	x	x
Audiometry	x		
Ear Impressions	x		
Administer Medical Device	x	x	
Primary Variable (speech testing)		x*	x*
Secondary Variables (APHAB)	x	x	
Secondary Variables (product questionnaire)	x	x	
Other Variables (preference questionnaire)			x
Adverse Events	x	x	x

*Randomization of lab trial test conditions

9.2 Assessments of outcomes

9.2.1 Assessment of primary outcome

The primary outcome is the objective speech testing results of the IMD compared with the RMD. Speech will be tested with the RMD and the IMD at the second and third appointments. Two speech tests, the OLSA and the GÖSA, will be used and with three conditions: unaided, aided with the RMD, and aided with the IMD.

9.2.2 Assessment of secondary outcomes

The overall performance of the IMD versus the RMD will be subjectively measured using a standardized questionnaire (APHAB) and two in-house questionnaires (product and preference). The subjects will rate the RMD using the APHAB and the IMD using the APHAB. The results from the two APHAB questionnaires will be compared. The product questionnaire will also be answered for both the RMD and IMD and the results compared. At the end of the trial the participants will be asked to complete a preference questionnaire where they shall choose either the RMD or the IMD as their preferred hearing aid and explain the reason for their choice.

9.2.3 Assessment of safety outcomes

The product questionnaire will specifically ask questions about safety and unexpected noises/behaviour of the instruments. Unexpected behaviour includes unprovoked feedback, distorted sounds or artefacts, discomfort, spontaneous muting or shutting off, unexplained warning signals or beeps, and loud sounds. This information provided from the subjects will alert the PI about any potential for safety risks that should be addressed before the product is released to the market. It is not expected that any of these things will occur and have not during testing on previous products.

9.2.3.1 Adverse events

For the recording of adverse events the subjects will be asked for a description of the event including how long it lasted, how many times it occurred, and if it caused discomfort or pain or a disruption of hearing ability. They will be recorded on the AE forms in the CRF.

9.2.3.2 Laboratory parameters

Not applicable

9.2.3.3 Vital signs

Not applicable

9.2.4 Assessments in participants who prematurely stop the study

After the study concludes the subjects will return the IMD. The follow-up procedure will be the same as for all active test subjects. They will be instructed to return to the clinic for any required maintenance or fine-tuning of their own devices. Those that prematurely withdraw from the study will still be wearing their own devices; therefore, their follow-up treatment will be the same as for the other participants that finish the study.

9.3 Procedures at each visit

9.3.1 Screening/First Visit

Screening visit, Day 0: The potential participants will be given the Patient Information and Informed Consent form. The trial will be explained including how many visits are expected as well as the type of testing that they will complete. They are given time during the appointment to decide whether to participate in the study. If they choose not to take part in the study they will not sign the consent form, and the appointment will finish. If they choose to join the trial they will sign and date the consent form. No trial activities will be performed before the consent form is signed and dated by the subject and the investigator. Subjects will receive a copy of the signed consent form. A hearing history is then taken and otoscopy is performed. A hearing test is performed and inclusion/exclusion criteria will be determined. An ear impression is taken of each ear to create the IMD, and the RMD programmed to a first fit and adjusted using REM data in order to better match the electroacoustic output of the RMD and the IMD. They are given two questionnaires (APHAB and product) to complete at home regarding

the RMD. They are scheduled for the second visit. Any AEs are reported in the CRFs.

9.3.2 Fitting/Second Visit

Fitting Visit, Day 10 +/-7: Otoscopy is performed, and the subjects are fitted with the IMD. Output of the IMD is measured, and the fitting adjusted, if necessary, to better match the electroacoustic output of the previously worn, RMD. They are randomized for the speech testing. Speech tests are made with the OLSA in three conditions: unaided, aided with RMD, and aided with IMD. The subjects return the RMD and held until the third appointment for further speech testing. The subjects return the completed questionnaires from the first visit and are given two more questionnaires (APHAB and product) to complete at home. They are given instructions about the IMD and an IFU with information about the IMD. They are scheduled for the third visit. Any AEs are reported in the CRFs.

9.3.3 Final/Third Visit

Final Visit, Day 28 +/- 5: The subjects will return the completed questionnaires. They are randomized for the speech testing. Speech tests are made with the GÖSA in three conditions: unaided, aided with RMD, and aided with IMD. They return the IMD and can continue to use their own BTEs as normal. The subjects will complete a preference questionnaire to determine if they preferred the IMD or the RMD. They are notified that the study has ended. They are given their reimbursement and instructed to continue using the clinic at Bernafon for routine device maintenance. Any AEs are reported in the CRFs.

10. SAFETY

10.1 Medical Device Category C studies

All adverse events (AE) including all serious adverse events (SAE) are collected, fully investigated and documented in the source document and appropriate case report form (CRF) during the entire study period, i.e. from patient's informed consent until the last protocol-specific procedure, including a safety follow-up period. Documentation includes dates of event, treatment, resolution, assessment of seriousness and causal relationship to device and/or study procedure.

The information on AEs is systematically collected by the clinician at each study visit. They will follow the procedures outlined in SOP-Medical Device Incident Reporting. The subjects are asked to keep a diary and write down any unexpected events. During the regular clinic visits the subjects are then asked questions about the event to gather details and to determine the severity of the event. If a subject reports pain that results in the inability to use the device he will be withdrawn from the study in order to avoid any pain from using the device and to remove partial data from the study. For reports of pain caused by insertion or the dome itself, the problem can be addressed in the clinic. For example, a different style or size of dome can be placed on the hearing aid, and re-training of insertion can be performed with the subject to avoid wrong or forceful insertion of the device. For reported pain they will be advised to not wear the device for 24 hours before resuming use.

Foreseeable adverse events outlined in the risk management file include discomfort caused by the domes, domes or filters falling off in the ear, no amplification coming from the device causing alarms or traffic to not be heard by the subject, skin reaction if chemical profile of device is changed, maximum output of the device exceeding 132 dB SPL, battery exploding or catching fire, and the device affecting other medical devices worn by the subject. The incidence of all of these risks or adverse events is improbable. To mitigate the risk, the IFU describes how to insert the device, how to change the domes, and how to change a battery in case of no amplification. The IFU describes how to clean the device, domes, and filters in order to not introduce cleaning agents that might change the chemical profile of the hardware of the device. The labelling warns of the potential maximum output of the device. The IFU instructs the user to keep the device away from explosive environments, The IFU warns of interference with implantable devices.

10.1.1 Definition and Assessment of (Serious) Adverse Events and other safety related events

Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in participants, users or other persons whether or not related to the investigational medical device [ISO 14155: 3.2].

This includes events related to the IMD or the RMD and to the procedures involved. For users or other persons this is restricted to events related to the IMD.

Adverse Device Effect (ADE)

Adverse event related to the use of an investigational medical device [ISO 14155: 3.1].

This includes any adverse event resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, operation, or any malfunction of the investigational medical device. This includes any event that is a result of a use error or intentional misuse.

AEs/ADEs include:

- Exacerbation of a pre-existing disease or condition.

- Increase in the frequency or intensity of a pre-existing episodic disease or medical condition.

- Any disease or medical condition detected or diagnosed after treatment with the study intervention device even though it may have been present yet undetected prior to the start of the clinical investigation.

- Any continuous persistent disease or symptoms present at baseline that worsen following the start of the clinical investigation.

- Events considered by the investigator to be related to any of the clinical investigation-mandated procedures.

- Abnormal assessments, e.g. physical examination findings, will be reported as AEs/ADEs if they represent a clinically significant finding that was not present at baseline or that has significantly worsened during the course of the clinical investigation.

- Test abnormalities will be reported as AEs/ADEs if they represent a clinically significant finding, symptomatic or not, which was not present at baseline or has significantly worsened during the course of the clinical investigation.

AEs/ADEs do not include:

- Pre-planned interventions or occurrences of endpoints specified in the CIP are not considered AEs/ADEs, if not defined otherwise.

- Unrelated medical or surgical procedures, e.g. surgery, endoscopy, tooth extraction, transfusion. However, the event leading to the procedure may be considered an AE. If this event is serious, the procedure will be described in the SAE/SADE narrative.

- Any pre-existing disease or medical condition that remains stable and does not worsen during the course of study participation.

- Situations in which an adverse change did not occur, e.g., hospitalizations for unrelated cosmetic elective surgery or for social and/or convenience reasons.

Serious Adverse Event (SAE)

Adverse event that:

- results in death, or
- led to a serious deterioration in health that either:
- results in a life-threatening illness or injury, or
- results in a permanent impairment of a body structure or a body function, or
- required in-patient or prolonged hospitalisation, or
- results in medical or surgical intervention to prevent life threatening illness, or
- led to fetal distress, death or a congenital abnormality or birth defect. [ISO 14155: 3.37].

This includes device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system. A planned hospitalization for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered to be a serious adverse event.

Device deficiency

Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labelling [ISO 14155: 3.15].

Health hazards that require measures

Findings in the trial that may affect the safety of study participants and, which require preventive or corrective measures intended to protect the health and safety of study participants [ClinO Art. 37].

Severity of adverse events/adverse device effects

The severity of clinical AEs is graded on a three-point scale: mild, moderate and severe, and reported in the CRF. If the severity of an AE worsens during medical device administration, only the worst intensity should be reported on the CRF. If the AE lessens in intensity, no change in the severity is required.

Mild: Event may be noticeable to subject; does not influence daily activities; the AE resolves spontaneously or may require minimal therapeutic intervention;

Moderate: Event may make subject uncomfortable; performance of daily activities may be influenced; intervention may be needed; the AE produces no sequelae.

Severe: Event may cause noticeable discomfort; usually interferes with daily activities; subject may not be able to continue in the study; the AE produces sequelae, which require prolonged therapeutic intervention.

Causal Relationship of SAE [MEDDEV 2.7/3 revision 3, May 2015].

A causal relationship towards the medical device or study procedure should be rated as follows:

- **Not related:** The relationship to the device or procedures can be excluded.
- **Unlikely:** The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
- **Possible:** The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible.
- **Probable:** The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause.
- **Causal relationship:** The serious event is associated with the investigational device or with procedures beyond reasonable doubt.

Device deficiencies that might have led to an SAE are always related to the medical device.

10.1.2 Reporting of (Serious) Adverse Events and other safety related events

Reporting to the Sponsor

The following events are to be reported to the Sponsor within 24 hours upon becoming aware of the event:

- All SAEs
- Health hazards that require measures
- Device deficiencies

The Sponsor will evaluate SAEs with regard to causality and seriousness. Device deficiencies are assessed regarding their potential to lead to an SAE.

Reporting to Authorities:

In Category C studies it is the local Investigator's responsibility to report **serious adverse events** in Switzerland which are

- related or possibly related to the medical device under investigation
- related or possibly related to study procedures
  within 7 days to the local Ethics Committee. The Sponsor-Investigator reports within the same timeline to Swissmedic (incl. events from abroad).
- **Health hazards** that require measures are reported within 2 days

All in the trial involved other Ethical Committees receive all mentioned reportable SAEs and health hazards having occurred in Switzerland via the Sponsor-Investigator within the same timeline. All participating investigators are informed regarding the occurrence of a health hazard.

Periodic safety reporting

In Category C studies a yearly safety update-report is submitted by the Investigator to the Ethics Committee and by the Sponsor-Investigator to Swissmedic.

10.1.3 Follow up of (Serious) Adverse Events

The adverse event shall be followed by the PI until its resolution or until the adverse event is recognized as permanent or stable condition by the PI. Follow-up investigations may be necessary according to the PI's medical judgement. In this situation, the follow-up does not have to be documented in the CRF but must be noted in the source documentation.

In case of SAE / SADE the sponsor can be contacted following the list below. If the first person in the list cannot be timely contacted, the PI should try to contact the next and so on.

Contact order

Contact order	Name	Mobile	Office	E-Mail
1	Michael Ernst	+41 31 998 15 57	Head of SIV	mier@bernafon.com
2	Bruno Keller	+41 31 998 15 92	Senior Director	brke@bernafon.com

Table1. Contact information of the sponsor in case of SAE/SADE

11. STATISTICAL METHODS

The primary outcome is the objective speech testing results of the IMD compared with the RMD. It will be measured two times during the trial. Speech will be tested with the RMD and the IMD at the second and third appointments. Two speech tests, the OLSA (reference test) and the GÖSA, will be used and with three conditions: unaided, aided with the RMD, and aided with the IMD. Speech Reception Threshold (SRT) from a previous experiment (BF001-1611) with the RMD and the OLSA test will be used to determine the required sample size.

11.1 Hypothesis

There is little evidence from research literature and experience that with equivalent technology, the IMD might be superior to the RMD for speech reception thresholds. Benefit from a more closed fit might be partially compensated by the larger distance between microphone on the BTE placement. However, we can expect that the performance should be at least as good with the IMD.

SRT benefit expressed in terms of benefit with amplification ($SRT_{unaided}$ - SRT_{aided}), will be used as primary outcome in the following hypothesis and sample size calculation. As there is no technical motivation to find a benefit with the IMD, the tested hypothesis should therefore focus on the non-inferiority of the IMD compared to the RMD:

H0: average benefit with the IMD (μ_{IMD}) is not non-inferior to the average benefit with the RMD (μ_{RMD})

$$\mu_{IMD} \leq \mu_{RMD} - \delta$$

H1: average benefit with the IMD (μ_{IMD}) is non-inferior to the average benefit with the RMD (μ_{RMD})

$$\mu_{IMD} > \mu_{RMD} - \delta$$

where δ is the non-inferiority margin.

The non-inferiority margin determination follows the guidelines of Flight & Julious (2016). The non-inferiority margin is defined to be the clinical acceptable difference allowing us to conclude that there is no difference between the treatments. We will base our reflexion on SRT benefit from the validation of the RMD to satisfy the following requirements:

- Assay sensitivity, the RMD should provide a benefit over the unaided condition. This can be verified by the achieved mean benefit of +4 dB SNR (SD = 0.8 dB SNR).
- Constancy assumptions, the IMD will be tested in the same conditions and the eligibility criteria are similar between both studies.
- Minimized bias, to reduce the influence of results variability from natural fluctuation the difference between conditions is used rather than absolute SRT results.

From the reference study, a significant and audible difference could be found between the tested devices. This was also reflected by a difference of 1.3 dB SNR (SD = 1.6 dB SNR) in the SRT scores. The OLSA test manufacturer states that the precision to determine the SRT lies around 1 dB for within subject measures. We can therefore set the non-inferiority margin to 1 dB SNR which correspond to a little bit less than 80 % of an audible effect measured with the test. With a non-inferiority margin of 1 dB, we are still ensuring that the IMD has a positive effect over the unaided condition.

11.2 Determination of Sample Size

The results with the IMD and the RMD are collected on the same subject. SRTs are continuous and normally distributed data. We can therefore apply the sample size determination for mean difference

on one sample.

The formula to compute the sample size is:

$$n = \left(\frac{\sigma\left(z_{1-\alpha} + z_{1-\beta}\right)}{\delta}\right)^2$$

With n the sample size, σ the standard deviation from the population, δ the non-inferiority margin, α the type I error, and 1-β the power of the test.

With the following input: σ = 1.6 dB SNR, δ = 1 dB SNR, α = 0.05, and 1-β = 0.8, we will need a sample size of 16 to satisfy the test hypothesis.

11.3 Statistical criteria of termination of trial

A single statistical analysis is planned once all recruited subjects have completed the trial (per-protocol). No interim analysis is planned and no “stopping rules” are set form a statistical perspective. PI’s and clinician judgement are considered as reliable enough to stop the trial.

11.4 Planned Analyses

The analysis and documentation will be done by the statistician using R (version 3.4) a statistical software package. R “stats” package will be used for the confidence interval, non-inferiority, and Wilcoxon tests. Documentation of the analysis will be done with R Studio under R Markdown format.

Main outcome: speech reception threshold (SRT from OLSA and GÖSA)

SRTs from the OLSA test are measured during the second visit. OLSA data from a previous trial (BF001-1611) are used for the hypothesis definition, the non-inferiority margin, and the sample size calculation.

The rationale for the analysis is: paired t-tests usually test that the mean differences are zero. The non-inferiority test compares the difference to a non-zero quantity δ. The assumptions of the paired t-test are:

1. The data are continuous (not discrete).

2. The data, i.e., the differences for the matched-pairs, follow a normal probability distribution.

3. The sample of pairs is a simple random sample from its population. Everyone in the population has an equal probability of being selected in the sample.

SRTs from the GÖSA test are measured during the third visit. The GÖSA speech material is different than the OLSA, because it uses different vocabulary and presentation levels. The GÖSA contains short everyday sentences while the OLSA uses standardized, meaningless sentences. Collecting data from two different speech materials should help to generalize our findings. However, due to different test properties (Kollmeier et al., 2011), a separate analysis must be conducted with each test. As we don’t have reference data for the GÖSA test, we cannot compute a non-inferiority margin.. Therefore, the GÖSA analysis is planned as a secondary analysis and described in section 11.4.3.

11.4.1 Datasets to be analysed, analysis populations

Analysis population: a single group that had the same treatment (per protocol set).

The included subjects are experienced hearing aid users (minimum 6 months) with the same hearing aid model across the population. As hearing loss does not normally fluctuate, we assume that their hearing capabilities are stable over time and that the performance with a hearing aid can be compared over a longer period without any wash out period. Subjects’ individual auditory capacities (hearing loss degree, noise tolerance, speech recognition) vary, however the sample is considered as a homogenous population regarding their experience with the RMD. It will be ensured that the acceptance to generic amplification via hearing aids is not tested but an actual evaluation of the difference between the RMD and the IMD. A single assignment treatment will be considered representative of clinical intervention, i.e. when an experienced hearing aid user tests the ITE device.

11.4.2 Primary Analysis

Speech Reception Threshold (SRT) from the OLSA test will be measured under three test conditions: unaided, control (RMD), and test (IMD). Test condition order will be randomized using a Latin square design to control any potential order effect. The difference between control and test condition will be

compared to the non-inferiority margin to test for non-inferiority. The unaided condition will be used as control of the investigational device benefit if non-inferiority could not be shown.

11.4.3 Secondary Analyses

OLSA test:

Switching to superiority test will be considered as recommended by the CPMP (2001):

“If the 95% confidence interval for the treatment effect not only lies entirely above −M but also above zero then there is evidence of superiority in terms of statistical significance at the 5% level (P < 0.05). In this case it is acceptable to calculate the P value associated with a test of superiority and to evaluate whether this is sufficiently small to reject convincingly the hypothesis of no difference.”

Hearing loss degree and age will be added in post hoc analysis as covariables.

GÖSA test:

Speech Reception Threshold (SRT) from the GÖSA test will be measured under three conditions: unaided, control (RMD), and test (IMD). Test condition order will be randomized using a Latin square design to control any potential order effect. The benefit of amplification will be evaluated with both tested devices with exploratory analysis. The hypothesis is that there is a significant improvement of SRTs in the aided over the unaided condition with the GÖSA test.

11.4.4 Interim analyses

No interim analysis is planned according the test design.

11.4.5 Safety analysis

Safety analysis is foreseen to be accomplished by a questionnaire completed by the participants during the trial. Clinical judgement from the PI will be used for the safety evaluation.

11.4.6 Deviation(s) from the original statistical plan

Any deviation from the original protocol must be justified and reported in the final report. Post hoc analysis can be done on secondary outcomes and reported in the final report.

11.5 Handling of missing data and drop-outs

For missing data, the PI will contact the involved subject to evaluate the possibility of getting missing data from a questionnaire by post. If a test subject cannot come to the evaluation visit, after exhausting all the possibilities to reschedule a new one, the devices will be sent back per post. If a subject does not want to adhere to the protocol, he can easily switch back to his own devices and return the IMD.

Dropouts will not be replaced; therefore, extra subjects over the calculated sample amount will be included from the beginning to ensure enough completed cases with all data.

The analysis and report will include two separate sections. The first section is based on data from all recruited subjects (as the intention to treat ITT part) and the second section is based on the data from subjects that complete the entire protocol (per protocol PP). Demographical and audiological data (e.g. hearing loss thresholds, degree, and classification) will be available from all recruited subjects including the withdrawn subjects and will be analysed in the report.

12. QUALITY ASSURANCE AND CONTROL

The Sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs and Working Instructions. The PI is responsible for proper training of all involved study personnel.

12.1 Data handling and record keeping / archiving

Data will be documented on paper and archived with an electronic data management system. The subjects will be given numbers to maintain anonymity. There are also hard copies of subjects' charts that are kept in a locked file cabinet inside of the clinic room. Only the PI, statistician, Monitor, and Auditor will have access to the information. The information will always be archived under the identification number with a key to the identification codes stored in another location (described in chapter 2.8).

12.1.1 Case Report Forms

Participant identities are coded using a participant identification number.

The PI will enter protocol defined data into a web based Electronic Case Report Forms using an EDC-software that conforms to 21 CFR Part 11 (FDA guidance) requirements. Site staff will be given access to the EDC system after a training. The data are checked automatically for plausibility and discrepancies. The generated appropriate error messages, allow the data to be confirmed or corrected before being saved in the database. At the end of the study, the PI must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the PI will receive a CD-ROM or paper copies of the patient data for archiving at the site.

The CRF contains the following information:

Field	Author
Date of examination	PI
Subject birth year	
Participant identification number	PI
Age	PI
Sex	PI
Otoscopy	
Standard audiometry	
Hearing loss classification	
Eligibility	
Trial information provided	
Date of Informed Consent	PI
Inclusion / Exclusion Criteria	PI
Ear disease	PI
Control hearing device serial numbers	PI
Real ear measure	
ITE order	
Investigational device serial numbers	PI

Results from GÖSA	PI
Results from OLSA	PI
Questionnaires received	
Questionnaires returned	
Devices returned	
IFU received	
Results from APHAB questionnaire	PI
Results from preference questionnaire	PI
Results from product questionnaire	PI
AEs / SAEs, ADE / SADE	PI
Next appointment	
Name, date, signature of PI	PI

12.1.2 Specification of source documents

The Principle Investigator will maintain adequate and accurate records to enable the conduction of the study to be fully documented and the study data to be subsequently verified. These documents will be classified into two different categories: PI's file, and subject clinical source documents. There will be a PI file or Investigator Site File (ISF) as well as corresponding subject files with source documents.

The PI's file will contain the CIP/amendments, IB/Instructions for use, CRFs, site standard operation procedures (SOPs) or reference to it, EC and CA approval with correspondence, informed consent, device records, staff curriculum vitae and authorization forms, screening and enrolment logs, site-specific subject identification code logs, and other appropriate documents/ correspondence as required by EN ISO 14155 and local regulations.

Subject clinical source documents include, but are not limited to subject hospital/clinic records, physician's and nurse's notes, appointment book, hearing test results, questionnaires, consultant letters, etc.

These two categories of documents must be kept on file by the PI for 10 years. If source documents are not durable as long as needed they must be preserved as a copy. When source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the site. The information will always be archived under the identification number with a key to the identification codes stored in another location (described in chapter 2.8).

For each subject enrolled an encoded electronic CRF must be completed and e-signed by the PI. This also applies to those subjects who fail to complete the study. If a subject withdraws from the study, the reason must be noted on the CRF.

Case report forms are to be completed immediately after the visit.

CRF entries and corrections will only be performed by study site staff, authorized by the PI. All forms should be completed using a blue permanent pen and must be legible. Errors should be crossed out but not obliterated, the correction inserted, and the change initialed and dated by the PI, co-PI or other investigator.

The entries will be checked by the Monitor and any errors or inconsistencies will be checked immediately. The Sponsor will collect original completed and signed CRFs at the end of the study. A copy of the completed and signed CRFs will remain on site and archived.

12.1.3 Record keeping / archiving

All study data must be archived for a minimum of 10 years after study termination or premature termination of the clinical trial.

12.2 Data management

12.2.1 Data Management System

The CRFs in this trial are implemented electronically using a dedicated electronic data capturing (EDC) system. The EDC system is activated for the trial only after successfully passing a test procedure.

All data entered in the CRFs are stored on a Windows server in a dedicated database located in Biel.

12.2.2 Data security, access and back-up

The server hosting the EDC system and the database is kept in a locked server-room in Biel. Only the system administrators have direct access to the server. A role concept with personal passwords (site investigator, statistician, monitor, administrator etc.) regulates permission for each user to use the system and database as he/she requires.

All data entered into the CRFs are transferred to the database using Secure Sockets Layer (SSL) encryption. Each data point has attributes attached to it identifying the user who entered it with the exact time and date. Retrospective alterations of data in the database are recorded in an audit table. Time, table, data field, original value and altered value, and the person are recorded (audit trail).

A multi-level back-up system is implemented. Back-ups of the whole system including the database are run several times per day. The back-up-data are stored in a secure place on a different storage-server.

12.2.3 Analysis and archiving

At final analysis, data files will be extracted from the database into statistical packages to be analyzed. The database will be locked at this time, recorded in special archiving format and securely stored for at least 1 year. In addition, the PI will receive a CD-ROM of the trial data for archiving at the site.

12.2.4 Electronic and central data validation

Data can be entered into the database only after a check of completeness and plausibility. Furthermore, selected data points are cross-checked for plausibility with previously entered data for that participant.

12.3 Monitoring

The study site will be monitored by an employee of the Sponsor. A minimum of 3 visits will be performed; one site initiation visit, at least one routine monitoring visits and one close out visit. The number of routine monitoring visits will be increased if needed based on the course of the study. The first routine monitoring visit will take place shortly after at least 5 patients have been enrolled.

Source documents will be made available for the monitor and the principle investigator or a delegated and authorized person will be available during the visits to answer questions.

100% source data verification will be completed for 3 patients at the first interim visit. For any additional interim visits, another 3 patients of 100% source data verification will be completed at each visit.

Subject to SDV for all patients are:

Patient Informed Consent Form

Eligibility criteria

Diagnosis

Visit dates

Study intervention details related to:

Procedural success

Procedure date and time

(Serious) Adverse Events Device deficiencies

The content of Investigator Site File (ISF) will be checked during each monitoring visit.

12.4 Audits and Inspections

CEC as well as CA have the right to execute inspections at the study site. The Sponsor may at any time conduct an audit of the study site.

The study documentation and the source data/documents have to be made accessible to auditors/inspectors and questions have to be answered during audits/inspections. All involved parties must keep the participant data strictly confidential.

12.5 Confidentiality, Data Protection

Direct access to source documents will be permitted for the purposes of monitoring, audits and inspections and only authorized persons involved in those activities are allowed to have direct access to source documents and must keep participants data strictly confidential.

12.6 Storage of biological material and related health data

Not applicable – no biological samples taken.

13. PUBLICATION AND DISSEMINATION POLICY

Trial results will be communicated to participants at the end of the trial. The trial results primary purpose is for internal product validation to ensure safety and performance of the device. The results will be communicated to other relevant groups (e.g., via publication, reporting in results databases, and other internal data sharing arrangements) as needed and for the purpose of sharing scientific information within the industry. The only people with authorship eligibility will be those that worked on the trial including the PI, statistician, and any other clinicians involved in testing. Any plans for writing will not include access to the full protocol but a description of it as well as a description of the participants. Statistics will be described sufficiently so that the reader understands the analysis and any conclusions made from it. Ultimately the decision to submit the report for publication and the ultimate authority over any of the activities is held by the Sponsor, Bernafon.

14. FUNDING AND SUPPORT

14.1 Funding

The Sponsor will financially support the trial including providing the clinic and all materials needed to complete the testing. This includes the devices themselves as well as equipment.

15. INSURANCE

Insurance will be provided by the Sponsor. A copy of the certificate is filed in each investigator site file and the trial master file.

16. REFERENCES

Provide a list of the references cited in the protocol.

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3. International Conference on Harmonization (ICH, 1997) E8 Guideline: General Considerations for Clinical Trials http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E8/Step4/E8_Guideline.pdf)
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17. Kollmeier, B., Lenarz, T., Winkler, A., Zokoll, M. A., Sukowski, H., Brand, T., & Wagener, K. C. (2011). Hörgeräteindikation und -überprüfung nach modernen Verfahren der Sprachaudiometrie im Deutschen. *HNO*, *59*(10), 1012–1021.
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17. APPENDICES

1. Medical Devices: IB (according to ISO 14155)
2. Medical Devices: Assurance of producer
3. Medical Devices: List of norms (vollständig eingehaltene, teilweise eingehaltene)
4. Case Report Form (e.g. CRF)
5. Patient Information and informed consent
6. Instructions for Use
7. Meta-Analysis

1. Medical Devices: IB (according to ISO 14155)
2. Medical Devices: Assurance of producer
3. Medical Devices: List of norms (vollständig eingehaltene, teilweise eingehaltene)
4. Radiolabelled products: Strahlenschutzverordnung
5. Case Report Form (e.g. CRF)
6. Patient Information and informed consent
7. Instructions for Use
8. List of study sites / PIs