Clinical Investigation Plan

Investigation Title: A retrospective mapping of health care utilisation and current quality of life status in adult subjects with a history of chronic otitis media with or without cholesteatoma who have undergone a primary tympanoplasty

Short Title:	MapCOM
CIP Number:	CBAS5780
Date:	Refer to system version control
Sponsor	Cochlear Bone Anchored Solutions AB Konstruktionsvägen 14 PO Box82 Mölnlycke 435 22 SWEDEN

This clinical investigation shall be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki, International Standard ISO 14155 Clinical investigation of medical devices for human subjects - Good Clinical Practice, and any regional or national regulations, as applicable.

Manufacturer	Not applicable
Sponsor Organisation	Cochlear Bone Anchored Solutions AB Konstruktionsvägen 14 PO Box82 Mölnlycke 435 22 SWEDEN
Coordinating Investigator	[redacted]
Clinical Research Organisation **(for monitoring of German and French sites only)**	[redacted]
Safety Contact	Not applicable
Statistics	Cochlear Bone Anchored Solutions AB Konstruktionsvägen 14 PO Box82 Mölnlycke 435 22 SWEDEN

A complete list of participating Principal Investigators' names, titles and addresses, and the names and addresses of participating institutions (sites) will be maintained by the Sponsor and will be provided as a separate Principal Investigator List. The definitive Principal Investigator list will be provided in the Clinical Investigation Report.

INVESTIGATOR AGREEMENT

Coordinating Investigator Approval and Declaration

By my signature below, I confirm my review and approval of this Clinical Investigational Plan (CIP).

I also confirm that I will strictly adhere to the requirements therein and undertake to ensure that all staff with delegated responsibilities in the conduct of this CIP have read, understood and will strictly adhere to the requirements therein. This CIP will not be implemented without prior written approval from the Ethics Committee, any applicable National Competent Authorities, and the Sponsor. If amendments to this plan become necessary, written approval by the Ethics Committee and any applicable National Competent Authorities will be obtained before the changes are clinically implemented per the amendment, except under emergency circumstances to protect the rights, safety, and well-being of subjects.

Name	**Title**
[redacted]	Coordinating Investigator
Signature	**Date**

Principal Investigator Declaration

By my signature below, I confirm that I have read, understood and will strictly adhere to the requirements therein. I undertake to ensure that all staff with delegated responsibilities in the conduct of this CIP have also read, understood and will strictly adhere to the requirements therein. This CIP will not be implemented without prior written approval from the Ethics Committee, any applicable National Competent Authorities, and the Sponsor. If amendments to this plan become necessary, written approval by the Ethics Committee and any applicable National Competent Authorities will be obtained before the changes are clinically implemented per the amendment, except under emergency circumstances to protect the rights, safety, and well-being of subjects.

Name	**Title**
	Principal Investigator
Site Name	**Site Address**
Signature	**Date**

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1 DEFINITIONS AND ABBREVIATIONS

Term	Description
ABG	Air Bone Gap
CBAS	Cochlear Bone Anchored Solutions AB
CHL	Conductive Hearing Loss
COM	Chronic Otitis Media
COMOT	Chronic Otitis Media Outcome Test
CRF	Case Report Form
CRO	Contract Research Organisation
CSOM	Chronic Suppurative Otitis Media
DCF	Data Clarification Form
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ENT	Ear, nose and throat
GCP	Good Clinical Practices
GNP	Gross National Product
HL	Hearing Level
HRQoL	Health-Related Quality of Life
HUI	Health Utilities Index
ICD-10	International Statistical Classification of Diseases and Related Health Problems – Tenth Revision
ICF	Informed Consent Form
MERI	Middle Ear Risk Index
MHL	Mixed Hearing Loss
OM	Otitis Media
PI	Principal Investigator
PORP	Partial Ossicular Replacement Prosthesis
QoL	Quality of Life
SAP	Statistical Analysis Plan
SSQ	Speech, Spatial and Qualities of Hearing Scale
TORP	Total Ossicular Replacement Prosthesis

2 CLINICAL INVESTIGATION SYNOPSIS

Investigation title	A retrospective mapping of health care utilisation and current quality of life status in adult subjects with a history of chronic otitis media with or without cholesteatoma who have undergone a primary tympanoplasty
Short title	MapCOM
Investigation number	CBAS5780
Name of investigational medical device(s)	Not applicable
Intended use of investigational medical device(s)	Not applicable
Name and description of comparator device/product(s)	Not applicable
Estimated recruitment period	Q1 2022 – Q1 2023
Expected duration per subject	The time it takes for the subject to receive, complete and return the informed consent form and the questionnaires and survey. Time for completing the questionnaires is estimated to be 30-40 minutes.
Number of subjects planned	200 subjects
Number of investigational sites planned	6-9 sites
Inclusion criteria	1. Adult subjects, 18 years or older. 2. Subjects with conductive or mixed hearing loss. 3. Subjects with historically documented diagnosis of Chronic Otitis Media (COM) with or without cholesteatoma in the operated ear. 4. Subjects who have undergone primary tympanoplasty type I-V to improve hearing between 2010-2016. 5. Subjects with a PTA4 air-bone gap ≥30 dB OR PTA4 air-bone gap between 25-30 dB with an air conduction threshold PTA4 ≥40 dB HL within 12 months after primary tympanoplasty in the operated ear. 6. Subjects who have been recommended by their health care professional to try a hearing aid to improve hearing in the operated ear. 7. Pre-op audiogram, maximum 1 year prior to the primary tympanoplasty, and post-op audiogram for the primary tympanoplasty are available. 8. Aided audiogram, unaided if no hearing device is used, available between 2018 and the point of enrolment. 9. Subjects are fluent in the language used for study questionnaires: German, French, Spanish. 10. Subjects are willing and able to provide written informed consent.

	11. Medical Record data is available throughout the defined data search period, from primary tympanoplasty to point of enrolment.
Exclusion criteria	1. Subjects are unable or unwilling to comply with the requirements of the study as determined by the investigator. 2. Investigator site personnel directly affiliated with this study and/or their immediate families; immediate family is defined as a spouse, parent, child, or sibling. 3. Cochlear employees or employees of Contract Research Organizations or contractors engaged by Cochlear for the purposes of this study.

Objectives and Endpoints	
Primary Objective	**Primary Endpoint**
Map health care utilisation.	Categorical data collected from primary tympanoplasty to time of enrolment: - Number and type of contacts with health care providers - Number and type of interventions and/or procedures (medical examinations, surgical procedures, hearing rehabilitation) - Number and type of medications and therapies
Secondary Objectives	**Secondary Endpoints**
Characterise long-term hearing performance.	Pre- and post-primary tympanoplasty and a third assessment between 2018 and time of enrolment: - PTA4 (0.5, 1, 2 and 4 kHz) for both air and bone conduction, under unaided and when applicable aided conditions.
Estimation of health care costs.	From primary tympanoplasty to time of enrolment: - Unit cost
Collect socio-economic data, demographics and information on service utilisation.	At time of enrolment: - Client Service Receipt Inventory (CSRI).
Assess patient reported outcomes.	At time of enrolment: - Health Utilities Index Mark III (HUI3) - Chronic Otitis Media Outcome Test-15 (COMOT-15) - Speech, Spatial and Qualities of Hearing Scale (SSQ-12)
Validate the COMOT-15 in French and Spanish.	Responses from a minimum of 30 subjects per language and audiograms collected within one year of questionnaire completeness.

Exploratory Objectives	Exploratory Endpoints
Develop scoring system to classify severity of middle ear status and relate to surgical outcome.	Middle Ear Risk Index factors (preoperative status, intraoperative findings) and surgical outcomes, if available.
Estimation of productivity losses.	Data on employment status collected in the CSRI survey used to determine the number of lost working hours as a result of COM.

3 SCHEDULE OF EVENTS

	Stage 1	Stage 2	Stage 3	Stage 4
Screening	Screening Medical Records for eligibility criteria			
Data collection		Informed consent	Questionnaires and survey (HUI3, COMOT-15, SSQ-12, CSRI).	Information from Medical Records (for complete list see Appendix 1)
Where	At clinic	At subject´s home or at clinic if a routine appointment is taking place during study period.	At subject´s home or at clinic if a routine appointment is taking place during study period.	At clinic
Timing of data collection	NA	NA	After signed informed consent	After signed informed consent
Performed by	Site personnel	Investigator + Subject	Subject	Site personnel

4 BACKGROUND INFORMATION AND RATIONALE

4.1 Introduction

Otitis media (OM) is an umbrella term used to describe inflammatory diseases of the middle ear, including acute OM, which may develop into chronic OM (COM) (1). COM subtypes are categorized as H65-H67 under International Statistical Classification of Diseases and Related Health Problems – Tenth Revision (ICD-10). COM is associated with the development of cholesteatomas (2), which are benign slow-growing tumours that develop in the middle ear space. Middle ear cholesteatomas are categorized under ICD-10 code H71 and are linked to poor patient outcomes since they can erode the middle ear space and middle ear ossicles (3). Global prevalence data show that 65–330 million individuals suffer from COM and that 60% of these individuals have significant hearing impairment (4). COM is characterized by recurring inflammation of the middle ear and mastoid cavity and may clinically present as otorrhea due to tympanic perforation in cases of chronic suppurative otitis media (CSOM) (5). The disease is normally triggered by an acute infection of the middle ear during

childhood (6). The World Health Organization defines OM to be chronic following two weeks of otorrhea, whereas other clinical guidelines generally consider that acute OM be classified as COM when patients with tympanic perforations continue to discharge mucoid material for a time period of greater than six weeks to three months, despite medical intervention (7). Recurrent COM can occur due to a combination of several factors and is a significant health burden that affects patient quality of life (QoL) (8). COM is one of the most prevalent global chronic infectious diseases and may lead to hearing impairment (9), including both conductive hearing loss (CHL) and mixed hearing loss (MHL). One of the major causes of COM-associated hearing loss is ossicular discontinuity (10). Hearing losses may range from 20 to 60 dB hearing level (HL) and may be irreversible (11, 12). In children, the resulting hearing loss can negatively impact their speech development, their ability to learn and their behaviour (13, 14). COM in adults has been linked to significantly lower levels of QoL and is associated with anxiety and depression (15). Furthermore, if unsuccessfully treated, several life-threatening complications may arise, including brain abscesses and meningitis (16).

4.1.1 Treatment interventions

COM is a multifactorial disease that is difficult to treat as it can be caused by various mechanisms and co-infections with more than one type of bacteria and/or virus (17). COM treatments principally aim to eradicate infection and restore a healthy middle ear cavity. Current treatment methods include a combination of earwax removal and topical and systemic antimicrobials to eliminate the infection. Surgical interventions include mastoidectomy and reconstruction of the tympanic membrane (18) in order to remove infected tissue and improve hearing (4). Cholesteatomas and ossicular discontinuities typically require a combination of more invasive and complex surgeries that aim to remove tissue overgrowth or to repair and reconstruct the damaged middle ear ossicles through ossiculoplasty. The total ossicular replacement prosthesis (TORP) and partial ossicular replacement prosthesis (PORP) are the two most common types of ossicular chain reconstruction surgeries. However, each surgery is associated with complications and risk of permanent hearing damage (19). Surgical results are also poorly reported and there is a large variation in surgical descriptions and outcomes described in the literature (20). Additionally, clinics in developing countries may not have access to the most modern surgical methods.

4.1.2 Hearing outcomes

Studies use several assessment methodologies and the overall clinical benefits of individual treatments in restoring hearing have not been systematically assessed, particularly not over the long-term. It is frequently reported that surgeries result in non-discharging ears, but it is also obvious that there is a subset of patients who do not show satisfactory improvements in hearing performance following surgery and that post-operative hearing outcomes in some patients actually deteriorate (21, 22). The condition of the ossicular chain is of key importance to hearing outcomes. A retrospective study of 213 patients demonstrated that an intact ossicular chain is significantly associated with improved long-term hearing outcomes after tympanoplasty for perforated COM (23). Patients with a compromised ossicular chain are likely to benefit from bone conduction hearing aids following mastoidectomy (24). It is crucial to understand how surgical intervention could affect hearing since there is extensive evidence of mild to moderate CHL in COM patients before surgery (25). These patients are also predisposed to developing MHL as the disease progresses (26). Studies also stress the need for performing audiometry to assess the patients' type and degree of hearing loss prior to treatment intervention since this is not routinely completed (27). Finally, even when audiometry is performed the methodology varies, making an accurate comparison difficult.

4.2 Findings of Previous Nonclinical and Clinical Studies

4.2.1 Nonclinical Data

No relevant non-clinical data is available.

4.2.2 Clinical Data

A systematic review investigating long-term hearing outcomes in COM patients treated under the current standard of care has been undertaken (28). The systematic review assessed literature published between 2008-2018 in order to assess the clinical success rate of COM treatments in restoring hearing loss (based on an air-bone gap (ABG) closure within 20 dB) at a minimum follow up time of 12-months in both adult and paediatric patients. Key outcomes from the systematic literature review indicated that 30.0% of patients have a post-operative air bone gap of ≥20 dB. Data also show that 14.7% of patients have post-operative complications, including 7.0% of patients in which a perforation of the tympanic membrane persisted at long-term follow up.

4.3 Study Rationale

The rational for conducting this primarily descriptive study is to broaden the understanding of the treatment pathways and health care interventions that follow a primary tympanoplasty (middle ear reconstructive surgery) among patients with COM, with or without cholesteatoma. An improved understanding of the treatment pattern will guide clinicians in making well-informed treatment decisions in order to improve the hearing and QoL of patients and more efficiently utilise available health care resources.

5 MEDICAL DEVICE INFORMATION

5.1 Identity and Description of the Investigational Medical Device (IMD)

Not Applicable.

5.2 Identity and Description of the Comparator

Not Applicable.

5.3 Accessory Device Requirements

Not Applicable.

6 OBJECTIVES

6.1 Primary Objective

1. Map health care utilisation.

6.2 Secondary Objectives

1. Characterise long-term hearing performance.
2. Collect socio-economic data, demographics and information on service utilisation.
3. Estimation of health care costs.

4. Assess patient reported outcomes.
5. Validate the COMOT-15 in French and Spanish

6.3 Exploratory Objectives

1. Develop scoring system to classify severity of middle ear status and relate to surgical outcome.
2. Estimation of productivity losses.

7 DESIGN OF THE CLINICAL INVESTIGATION

7.1 General

This is *primarily a retrospective study* to evaluate the standard of care of patients with COM across three countries in Europe. The study is therefore set up as a multicentre clinical investigation with a retrospective part (medical record review) and a minor prospective element with questionnaires and a survey completed by the subjects.

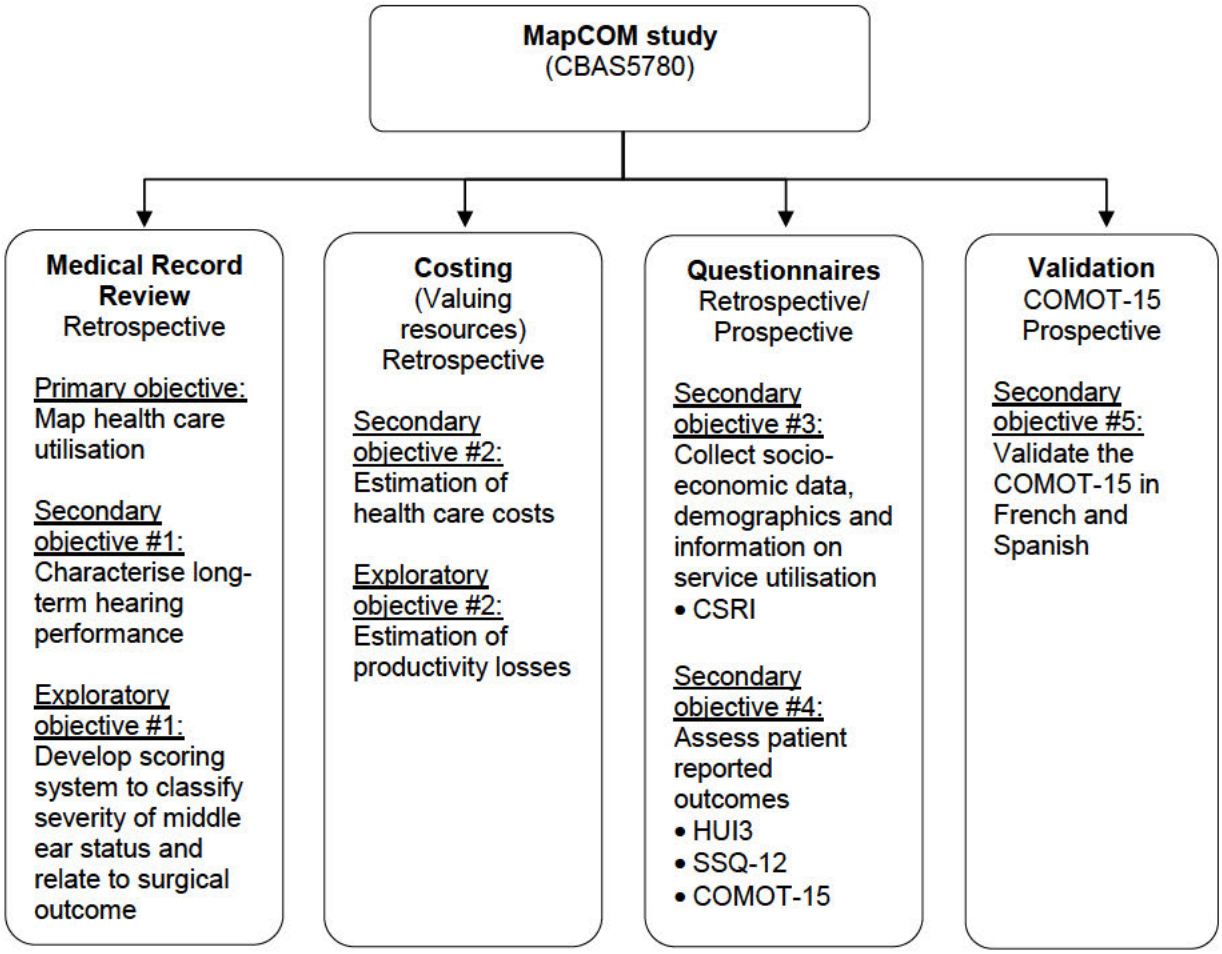

Figure 1: Schematic illustration of the clinical investigation elements

The subjects shall include men and women aged 18 years or older who underwent primary tympanoplasty to improve hearing between 2010-2016 and have a historically documented diagnosis of COM, with or without cholesteatoma in the operated ear. Subjects will be screened and 200 subjects will be enrolled in the clinical investigation across the 6-9 investigation sites in Germany, Spain and France. The study will aim to enrol subjects with an even distribution across all study sites. If any site has difficulties with recruitment the remaining sites can recruit more subjects, so the total recruitment is not affected, upon agreement with the Sponsor. In view of a possible situation where last recruitment efforts may result in exceeding the needed 200 subjects, no more than 10% over recruitment is expected.

In case no other follow-up visit to the clinic is planned within the study recruitment period subjects who have had an audiogram done between 2018 and the point of enrolment will be sent the ICF, questionnaires and survey via registered mail for completion at home. Subjects who are planned to have a follow-up audiogram collected within the study recruitment period will be asked to complete the ICF, questionnaires and survey at the time of their appointment. The medical record search for data extraction will be done at the clinic. See section *3. Schedule of Events*.

The primary endpoint is to collect categorical data; number and type of contacts with health care providers, number and type of interventions and/or procedures and number and type of medications and therapies to map health care utilisation. Health care utilisation data will be analysed in patient years, from primary tympanoplasty to point of enrolment. Secondary endpoints are PTA4 to give information about hearing performance, unit cost for an estimation of health care costs, CSRI survey to collect socio-economic data, demographics and information on service utilisation, questionnaires (HUI3, COMOT-15, SSQ-12) to assess current patient reported outcome and responses from a minimum of 30 subjects per language (29) and audiograms collected within one year of questionnaire completeness to validate COMOT-15 in French and Spanish. Exploratory endpoints are data on employment status for an estimation of productivity losses and Middle Ear Risk Index factors and surgical outcome to develop a scoring system to classify severity of middle ear status and relate to surgical outcome, if needed information is available.

7.1.1 Design Rationale

This study is designed to collect information regarding health care interventions that follow a primary tympanoplasty with residual hearing loss among adult subjects with diagnosis of COM, with or without cholesteatoma. A multicentre set-up is necessary to accurately capture the standard of care as this can vary at each site, as determined by treatment practice surveys at potential sites and it is important that we capture outcomes on all potential interventions that may be offered as part of standard care. The rationale to collect information from subjects who underwent a primary tympanoplasty procedure between 2010-2016 is to increase the likelihood of availability of electronic medical records data as these systems have only typically been introduced in recent years. This inclusion time frame is also important to capture the current standard of care rather than outcomes from obsolete procedures and to find enough subjects that have at least five years follow-up data so that we may capture patients who have reached a steady state. Subjects with single-sided deafness are not eligible for the study as COM with or without cholesteatoma leads to mainly conductive or mixed hearing loss. Paediatric subjects are excluded from the study as tympanoplasties are delayed until adulthood in some clinics.

7.2 Subjects

Written informed consent must be obtained from the subject or its legally authorised representative before any data is collected.

Eligibility of subjects must be supported by the inclusion and exclusion criteria listed below.

7.2.1 Inclusion Criteria

Subjects must meet all of the inclusion criteria described below to be eligible for this clinical investigation.

1. Adult subjects, 18 years or older.
2. Subjects with conductive or mixed hearing loss.
3. Subjects with historically documented diagnosis of Chronic Otitis Media (COM) with or without cholesteatoma in the operated ear.
4. Subjects who have undergone primary tympanoplasty type I-V to improve hearing between 2010-2016.
5. Subjects with a PTA4 air-bone gap ≥30 dB OR PTA4 air-bone gap between 25-30 dB with an air conduction threshold PTA4 ≥40 dB HL within 12 months after primary tympanoplasty in the operated ear.
6. Subjects who have been recommended by their health care professional to try a hearing aid to improve hearing in the operated ear.
7. Pre-op audiogram, maximum 1 year prior to the primary tympanoplasty, and post-op audiogram for the primary tympanoplasty are available.
8. Aided audiogram, unaided if no hearing device is used, available between 2018 and the point of enrolment.
9. Subjects are fluent in the language used for study questionnaires: German, French, Spanish.
10. Subjects are willing and able to provide written informed consent.
11. Medical Record data is available throughout the defined data search period, from primary tympanoplasty to point of enrolment.

7.2.2 Exclusion Criteria

Subjects who meet any of the exclusion criteria described below will not be eligible for this clinical investigation.

1. Subjects are unable or unwilling to comply with the requirements of the study as determined by the investigator.
2. Investigator site personnel directly affiliated with this study and/or their immediate families; immediate family is defined as a spouse, parent, child, or sibling.
3. Cochlear employees or employees of Contract Research Organizations or contractors engaged by Cochlear for the purposes of this study.

7.2.3 Number of Subjects Required

200 subjects will be enrolled in the clinical investigation, with a maximum estimated overhead of 10% taking into consideration the simultaneous recruitment at all sites. It is estimated that approximately double the size will need to be screened (30) to meet this sample size. Additionally, to meet the

validation requirements on the COMOT-15, a minimum of 30 subjects (29) with complete data are required at both the Spanish and French clinics (see section 7.3.2.1 for detailed justification).

7.2.4 Vulnerable Populations

Not applicable.

7.2.5 Recruitment and Study Duration

The following subject status definitions apply:

- Enrolled: A subject that has signed the Informed Consent Form (ICF) for the study.
- Screen Fail: An Enrolled subject that has been determined to not meet one or more eligibility criteria.
- Participated: Subjects who have met eligibility criteria and have started on protocol defined events.
- Withdrawn: An Enrolled subject who withdrew or was withdrawn by the Investigator or Sponsor before the expected End of Study.
- Completed: Enrolled subjects who complete the required tasks and schedule.

The recruitment period for the clinical investigation is estimated to be approximately 12 months from the time of first subject enrolled to the last subject.

Recruitment of subjects shall be performed in a back-chronological order from the primary tympanoplasty surgery. Recruitment shall start with the last subject that has undergone this procedure in the year 2016 and chronologically working backwards until recruitment targets are met. This process will avoid any recruitment bias.

The expected duration of each subject's participation in the clinical investigation is the time it takes for the subject to complete and return the ICF, questionnaires and survey. Time for completing the questionnaires is estimated to 30-40 minutes.

Clinical Investigation completion is defined as the recording and completion of the last medical record search for the last enrolled subject in the electronic Case Report Forms (eCRF).

7.2.6 Criteria for Subject Withdrawal

Subjects can decide to withdraw from the investigation at any time. The Investigator shall ask the reason(s). The reason for withdrawal (if available) should be documented in the subject's source files and the referent electronic case report form (eCRF).

The Investigator or Sponsor may also decide to withdraw a subject from the clinical investigation if it is considered to be in the subject's best interests.

Subject withdrawal may be for any of the following reasons:

- CIP or GCP deviation
- Subject withdrew consent
- Subject died

- Sponsor decision
- Investigator decision
- Other (specify)

If a subject is lost to follow-up, every possible effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation. At least 3 separate attempts taken to contact the subject must be documented.

Participating subjects who are withdrawn/discontinued will be replaced if medical record search is not completed.

7.2.7 Randomisation Procedures

Not applicable.

7.2.7.1 Blinding Procedures

Not applicable.

7.2.8 Post-investigation Medical Care

No specific care will be provided for the subjects after this study has been completed.

7.3 Performance Evaluations and Procedures

7.3.1 Eligibility evaluations and Procedures

Screening of subjects include searches by site personnel in medical records for inclusion and exclusion criteria.

The search for a primary tympanoplasty to improve hearing can include any primary tympanoplasty of types I-V based on the Wullstein classification (31).

Eligible subjects will be included chronologically based on date of primary tympanoplasty, from most recent to least recent. In a first draw, the number of subjects intended to be enrolled at a site plus 20% (to account for non-responders) will be contacted. To confirm that subjects are alive before they are contacted, a search in public death records should be performed according to local regulations and practices.

Subjects will first be contacted via mail or by phone. If they agree to receive a consent form, this will either be sent to them by mail or shared directly at the clinic if they are scheduled for an appointment. The subject has the right to have sufficient time to read the consent, ask questions and have those questions answered by the site personnel responsible for consent. When the consent form is signed by the subject at home, it will be sent back to the clinic by registered mail using a pre-filled and stamped envelope with the address of the clinic. The date of the consent discussion will be documented in the informed consent form and once this is signed by the responsible site staff, a copy of the mutually signed form will be shared with the subject.

If the number of targeted subjects at the clinic is not reached in a first draw, a second and potential third draws (in the same way as the first one) will be performed until the targeted number of subjects for the site is reached.

7.3.2 Participant Evaluations and Procedures

7.3.2.1 Study data – Questionnaires/survey

When a subject is enrolled in the investigation, data collection can start. In case subjects are due for a follow-up appointment at the clinic, as per standard of care, questionnaires and survey can be completed at site. For those subjects where an aided (unaided if no hearing aid used) audiogram between 2018 and point of enrolment is available, and who are not scheduled to any appointment at the clinic during the investigation period, questionnaires and survey (together with a copy of the mutual signed ICF) are sent via mail to be completed at home. All questions regarding the questionnaires and survey can be raised with the site personnel. If completed at home, questionnaires and survey shall be sent back to the clinic by registered mail using a pre-filled and stamped envelope with the address of the clinic.

The completeness of the questionnaires and survey will be verified by site personnel. Incomplete data will be followed-up with the subject, if answered at home by sending a copy of the questionnaire/survey back to the subject where incomplete parts requiring an answer are highlighted. If the questionnaires and survey are not returned; every possible effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation. At least 3 separate attempts taken to contact the subject must be documented.

The subjects will be asked to complete the following survey and questionnaires:

- Health care utilisation survey (adapted version of Client Service Receipt Inventory, CSRI)
- Health-Related Quality of Life – Health Utilities Index Mark 3 (HUI3)
- Chronic Otitis Media Outcome Test-15 (COMOT-15)
- Speech, Spatial and Qualities of Hearing Scale (SSQ-12 version)

<u>Health care utilisation survey</u>

The Adapted version of the Client Service Receipt Inventory (CSRI) (32), is a research instrument developed in the mid-1980s to collect information on primarily service utilisation and has been used in over 500 studies.

The CSRI can be used at multiple points within a study, thus tracking changes over time. The CSRI is also adaptable in administration. Although originally designed to be administered to the service user or their carer face to face with a trained interviewer, the CSRI has been successfully administered via post for the service user to be completed by themselves.

The adapted version of CSRI will, in this investigation, collect data referring to the 6 months before enrolment regarding demographics (marital status, cohabitation, usual place of residence, education level), medical history (chronic diseases, smoking status, date when first diagnosed with chronic ear infection, current middle ear issues, recurrent ear infections), hearing rehabilitation (current hearing aid or hearing device and category of hearing aid/device and hours per day of usage if applicable), health care utilisation related to ear infection and hearing difficulties (number of face-to-face consultations with care providers, investigations or diagnostic tests, number of in-patient admissions, medications) and employment information (employment status, inability to work in days/hours).

<u>Health-Related Quality of Life – Health Utilities Index Mark III (HUI3)</u>

HUI® is a generic preference-based system for measuring comprehensive health status and Health-Related Quality of Life (HRQoL) (33). HUI provides descriptive evidence on multiple dimensions of health status, a score for each dimension of health and an overall HRQoL score. The scoring systems provide utility (preference) scores on a generic scale where dead = 0.00 and perfect health = 1.00. HUI3 will be used in this study. The HUI3 classification system is comprised of 8 attributes: Vision, Hearing, Speech, Ambulation, Dexterity, Emotion, Cognition and Pain – each with 5 or 6 levels of ability/disability (34). The version in this clinical study uses a recall time of 1 week.

The license to use the HUI questionnaire is purchased from Health Utilities Inc., 88 Sydenham Street, Dundas, ON, L9H 2V3 Canada.

Speech, Spatial and Qualities of Hearing Scale (SSQ-12 version)

The Speech, Spatial, and Qualities of Hearing Scale questionnaire (SSQ-12) (35) was developed in the MRC Institute of Hearing Research, UK, and is a scaled-down version of the 49 items SSQ questionnaire (36). It is designed to compile a sub-set of items from the longer original 49 version to represent the scale as a whole, measuring self-reported auditory disability, reflecting the reality of hearing in the everyday world. It has been shown to provide similar results to SSQ-49 (35). It covers:

- Hearing speech in a variety of competing contexts
- The directional, distance and movement components of spatial hearing
- Segregation of sounds and attending to simultaneous speech streams
- Ease of listening
- The naturalness, clarity and identifiability of different speakers, different musical pieces and instruments, and different everyday sounds

Chronic Otitis Media Outcome Test-15 (COMOT-15) **and validation in French and Spanish**

The subjects will be asked to complete a Chronic Otitis Media Outcome Test-15 (37).

COMOT-15 is 15-item questionnaire that is a reliable and sensitive instrument for measurement of HR-QoL of subjects with COM.

The instrument consists of three subscales: ear symptoms (questions 1-6), hearing function (questions 7-9), and mental health (questions 10-13), which form the overall score (questions 1-13). In addition, one question on the general evaluation of the impact of COM on QoL (question 14) and one question to indicate the frequency of doctor visits in the last six months as a result of COM (question 15) are asked. The total score and the sub-scores are transformed to a 0-100 scale by dividing the sum of the raw scores of the items by the sum of spans of the items followed by multiplying by 100. Overall scores and sub-scores will be calculated for subjects based on this methodology, and compared between interventions, if feasible. COMOT-15 is validated in German and will be used in its original version at German-speaking clinics. For non-German speaking clinics, the COMOT-15 has been cross-translated and linguistically validated in Spanish and French by a certified translation agency (Software and Documentation Localization PLC) using published methodology (38). As the COMOT-15 is a COM-specific questionnaire that has already demonstrated reliability in additional languages, validation of the instrument in French and Spanish will require that

the questionnaire is completed by a minimum of 30 subjects per language, based on the accepted subject to item ratio of at least 2 (29).These subjects must have an accompanying audiogram (PTA4 at minimum) collected within 12 months of questionnaire completeness and completed the SSQ and HUI3 questionnaire as part of the investigation. Aided audiograms should be collected if the subject is using a hearing device. The widely accepted Cronbach's alpha value of 0.7 will be used as a cut-off to measure consistency.

7.3.2.2 Study data from medical records

The medical record search for data extraction can start in parallel to the questionnaires/survey being answered.

Data to be collected from the medical records include:

- Demographics and hearing/device history information
- Pre- and post-primary tympanoplasty air and bone conduction audiograms (unaided and when applicable aided and PTA4 at minimum)
- Latest available (as per inclusion criteria) air and bone conduction audiograms (unaided and when applicable aided and PTA4 at minimum)
- COM-related contacts with health care providers for the operated ear (including name and number of interventions and/or procedures, medications and therapies, examinations and Middle Ear Risk Index factors and surgical outcomes where applicable)

More details on the information to be collected can be found in **Appendix 1.**

It might be the case in a few sites, that the required audiograms for some subjects were collected in a hearing aid partner centre/shop and not in the clinic itself. For these situations, clinics will reach out to the responsible audiologist and request a copy of the test.

For analysis, health care contacts, interventions and/or procedures will be coded using the ICD-10 coding system. Medication will be coded according to WHO CC ATC.

7.4 Safety Evaluations and Procedures

Not applicable.

7.4.1 Concomitant Medication and Therapies

All medications and therapies related to COM and its rehabilitation which were prescribed during and from primary tympanoplasty must be recorded in the appropriate section of the eCRF.

7.5 Equipment Used for Evaluation of Performance and Safety

Not applicable.

7.6 Sponsor Role in Conduct of the Clinical Investigation

The Sponsor employees (or designee) shall use standard operating procedures to ensure that clinical study procedures and documentation are consistently conducted and compliant with Declaration of Helsinki and applicable parts of GCP and any regional or national regulations.

The Sponsor shall ensure that the study is quality controlled (monitored) by a monitor who is independent from the study, scientifically and clinically competent and has good knowledge of the study plan, ICF, sponsor´s SOPs, GCP and applicable laws and regulations.

The Sponsor shall monitor tasks delegated to other organizations/persons (Sponsors oversight) e.g. contract research companies (CRO) or other consultants.

The Sponsor is responsible for developing a study plan and compile a clinical study report when the study is completed.

The Sponsor shall make sure that electronic systems used in the study are validated, that a Trial Master File is created, subjects identity are coded so that reported data is coded but can be linked to the respective research person, that all essential study documentation is available in a safe place before, during and after the study according to applicable laws and regulations.

The Sponsor shall also make sure that the investigators have sufficient qualifications, enough resources are available at site, collect signed study plans from respectively responsible investigator and establish agreements with participating clinics.

It is the Sponsor´s responsibility to check that there is an EC approval for the study, to register the study in a public database and assure that the study results are reported within one year.

All study deviations will be documented in the CRF to enable analysis and reporting by the Sponsor in the Study Report, or to the relevant regulatory authority(s), if applicable.

8 RISKS AND BENEFITS OF THE INVESTIGATIONAL MEDICAL DEVICE AND CLINICAL INVESTIGATION

8.1 Anticipated Clinical Benefits

Participation in this study will not directly benefit the subject nor will it alter the subject´s course of care. However, information gained from the study may identify shortcomings in the current standard of care, which may be used to guide more effective interventions in the future.

Additionally, by collecting self-reported feedback via the questionnaires from the subjects, the clinical personnel can take the opportunity to identify potential needed follow-ups accordingly.

8.2 Anticipated Adverse Device Effects

Not applicable.

8.3 Risks Associated with Participation in the Clinical Investigation

Participation in the study will not alter the subject´s course of care. Sensitive data concerning the subject's health is being handled in the study. For subjects completing the ICF and questionnaires/survey at home, there is a risk that these documents might be lost in transit.

8.4 Risk Mitigation

All data collected will be pseudonymised and therefore the risk that any sensitive data will be disclosed to unauthorized persons is considered to be minimal. Registered post will be used when

sending ICFs and questionnaires/survey. For questionnaires/survey, clinical personnel will complete header with subject identification code and request that no personal data is shared on these documents, making them pseudonymised.

8.5 Risk-to-Benefit Rationale

The benefit of the clinical investigation of potentially identifying shortcomings in the standard of care and hence being able to guide more effective interventions in the future is regarded to outweigh the minimal anticipated risk for the subjects participating in the clinical investigation. We therefore consider it ethical to conduct the investigation.

9 STATISTICAL CONSIDERATIONS

9.1 General Considerations

Descriptive statistics will be used for analysis in this study. All analyses will be made on the full data set. All analyses will be presented as aggregated data without the possibility of identifying data from individual subjects.

9.2 Endpoints

9.2.1 Primary Endpoint

1. Categorical data collected from primary tympanoplasty to time of enrolment:
    - Number and type of contacts with health care providers
    - Number and type of interventions and/or procedures (medical examinations, surgical procedures, hearing rehabilitation)
    - Number and type of medications and therapies

9.2.2 Secondary Endpoints

1. Pre- and post-primary tympanoplasty and a third assessment between 2018 and point of enrolment:
    - PTA4 (0.5, 1, 2 and 4 kHz) for both air and bone conduction, under unaided and when applicable aided conditions.
2. From primary tympanoplasty to time of enrolment (analysed in patient-years):
    - Unit cost
3. At time of enrolment:
    - Client Service Receipt Inventory (CSRI)
4. At time of enrolment:
    - Health Utilities Index Mark III (HUI3)
    - Chronic Otitis Media Outcome Test-15 (COMOT-15)
    - Speech, Spatial and Qualities of Hearing Scale (SSQ-12)

5. Responses from a minimum of 30 subjects per language and audiograms collected within one year of questionnaire completeness.

9.2.3 Exploratory Endpoints

1. Middle Ear Risk Index factors (preoperative status, intraoperative findings) and surgical outcomes, if available.
2. Data on employment status collected in the CSRI survey used to determine the number of lost working hours as a result of COM.

9.3 Hypotheses

9.3.1 Primary Hypothesis

Not applicable.

9.3.2 Secondary Hypothesis

Not applicable.

9.3.3 Exploratory Hypothesis

Not applicable.

9.4 Sample Size Determination

The aim of this investigation is to map health care utilised by subjects with a history of COM, who have already had a primary tympanoplasty. Findings from this investigation will primarily help estimate the burden in terms of health care costs and impact on HRQoL that follows a first tympanoplasty for this subject population. As this study is not testing for differences in treatments or strengths of associations (primary objective is to map healthcare utilisation) then it is only necessary that the study is capable of capturing all potential interventions that may be offered as standard of care for the population. To ensure that enough medical records are sampled to capture all potential COM-related interventions included in the standard of care a sample size determination using published methods for calculating sample sizes in retrospective studies was undertaken (39). The calculation is based on the potential for patients with COM to receive the least likely intervention, which was determined to be a bone conduction solution, prescribed at a rate of 2.63% (unpublished registry data). Using these data, we estimate that 200 subjects are sufficient to capture the least likely intervention in at least four subjects, where the probability of observing this intervention at least once is 98% with a 95% confidence interval of 96-100% (Table 1).

Table 1. Expected number of subjects receiving treatment according to sample size.

		Results: Expected number of individuals receiving treatment; (Probability of observing treatment at least once); ± Expected 95% confidence interval width for proportion receiving treatment					
		Sample size					
		50	100	200	300	500	1000
Proportion receiving treatment	0,01	1 (0.39); +/-0.03	1 (0.63); +/-0.02	2 (0.87); +/-0.01	3 (0.95); +/-0.01	5 (0.99); +/-0.01	10 (1); +/-0,01
	0,02	1 (0,64); +/-0,04	2 (0,87); +/-0,03	4 (0,98); +/-0,02	6 (1); +/-0,02	10 (1); +/-0,01	20 (1); +/-0,01
	0,04	2 (0,87); +/-0,05	4 (0,98); +/-0,04	8 (1); +/-0,03	12 (1); +/-0,02	20 (1); +/-0,02	40 (1); +/-0,01
	0,08	4 (0,98); +/-0,08	8 (1); +/-0,05	16 (1); +/-0,04	24 (1); +/-0,03	40 (1); +/-0,02	80 (1); +/-0,02
	0,16	8 (1); +/-0,1	16 (1); +/-0,07	32 (1); +/-0,05	48 (1); +/-0,04	80 (1); +/-0,03	160 (1); +/-0,02
	0,32	16 (1); +/-0,13	32 (1); +/-0,09	64 (1); +/-0,06	96 (1); +/-0,05	160 (1); +/-0,04	320 (1); +/-0,03

9.5 Analysis Populations

Full analysis set consists of all subjects enrolled in the study.

9.6 Primary Endpoint Analyses

COM-related health care utilisation, collected from medical records, from date of primary tympanoplasty to point of enrolment (analysed in patient-years) and CSRI questionnaire referring to the six-months prior to completion will be cross-checked to ensure data accuracy. Any overlapping extracts will be analysed as a single extract. Data from medical records related to information on health care contacts and costs for each contact (detailed variables are presented below) will be used in the analysis. Care consumption in the form of contacts, diagnoses and costs will be analysed with a view to identifying cost factors. All comparisons will be presented as aggregated data without the possibility of identifying data for individual subjects. Data coding will permit care episodes (a series of care contacts of the same individual) to be identified so that health care consumption and costs can be calculated per individual subject.

Health care utilisation will be mapped per individual subject and sub-analysis will be performed based on intervention subtypes, if feasible.

Health care contacts, interventions and/or procedures will be coded by ICD-10 classification. Medications will be summarised by higher level anatomical therapeutic classification (ATC) group and generic term. Therapies will be listed but not coded.

9.7 Secondary Endpoint Analyses

Hearing performance

Audiogram data (see 9.2.2) collected pre- and post- primary tympanoplasty and between 2018 and point of enrolment will be compared to investigate how the standard of care impacts the subjects´ hearing, when feasible. Wilcoxon signed rank test will be used to compare the audiometric test results.

Survey - CSRI

Service utilization data collected through the CSRI will be used to map resource usage patterns for individual subjects and to determine associations between resource usage and socioeconomic status. Applicable events in medical history will be summarised using ICD-10 classification.

Health care costs

Direct medical costs associated to COM-related health care utilisation will be calculated for each subject using standard cost/unit in each participating country. Costs for individual contacts will be assigned with a view to identifying COM related health care cost factors for individual subjects and for groups of interventions, where feasible. All comparisons will be presented as aggregated data without the possibility of identifying data from individual subjects.

Estimation of costs will be based on primary outcomes that will be allocated a unit cost. The base case analysis will employ standard unit costs from all the included countries on the pooled data on utilisation and adjusted to the cost year 2022 and converted into Euros using the World Bank conversion factor for purchasing power parity. Health care costs in the population will be based on the health care consumption from primary tympanoplasty to enrolment (analysed in patient-years) and assumptions on when a state of stability is reached, which will be determined using data collected as part of this investigation itself.

Patient reported outcome

Attribute levels and scores will be calculated for individual subscales and general scores for each subject. If possible, data will also be grouped by intervention type and differences in scores between these groups will be analysed. Change in score will be assessed using the Wilcoxon rank sum test and sub-group analyses by age and gender may be performed, if feasible.

Validation of COMOT-15 in French and Spanish

The validated German version of the COMOT-15 that has been translated, back translated and linguistically validated will be used to validate the instruments reliability in French and Spanish. The instrument will be administered according to the original procedure and criterion validity will be assessed by comparing COMOT-15 scores with PTA4. COMOT-15 properties, including internal consistency will be assessed using Cronbach's alpha, where a value of >0.7 is indicative of acceptable reliability for clinical purposes.

9.8 Exploratory Endpoint Analyses

Middle Ear Risk Index factors

The Middle Ear Risk Index (MERI) will be used to guide the extraction of middle ear status variables from the medical records (40). If available, pre-operative factors collected from the medical records will be used to populate the MERI, generating a risk score for individual subjects by summing the corresponding risk factor scores defined within each section of the index. Subjects will be stratified into a low-medium-risk group (MERI: 0–7) and a high-risk group (MERI: 8–15). The relationship between pre-operative factors corresponding to those contained in the MERI on the success rate of tympanoplasty, based on post-operative ABG, will be investigated using a binary logistic regression model. The Spearman correlation coefficient will be used to determine relationships between pre-operative factors and their influence on post-operative outcomes.

Estimation of Productivity Losses

Employment history data will be collected from the CSRI survey and used to estimate productivity losses due to COM. Lost productivity will be estimated using the human capital approach, which measures lost productivity as the amount of time by which working life is reduced due to illness. To calculate productivity losses, lost working hours will be collected from the CSRI survey, valued at the market wage and adjusted to account for labour force participation and unemployment. Any hour not worked due to COM will be counted as an hour of productivity lost.

9.9 Safety Analyses

Not applicable.

9.10 Interim Analyses

Not applicable.

10 INFORMED CONSENT PROCESS

The Investigator shall obtain written informed consent from the subject as needed, using an approved ICF, prior to any data collection for the purpose of this investigation.

The rationale of the clinical investigation, as well as the risks and benefits, what participation will involve, and alternatives to participation will be explained to the subject. Enough time will be provided for the subject to enquire about details of the clinical investigation and to decide whether to participate.

All questions about the clinical investigation shall be answered to the satisfaction of the subject or the subject's legally acceptable representative. Subjects shall not be coerced or unduly influenced to participate or to continue to participate in a clinical investigation.

Each subject (or their legally authorised representative) and the person who conducted the informed consent discussion, shall sign and date the Informed Consent Form (ICF) accordingly. Where required, a witness shall sign and personally date the ICF. A copy of the signed ICF shall be given to the subject. The original signed ICF shall be archived in the Investigator's Site File at the investigational site.

The subject, or the subject's legally authorised representative, shall be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the clinical investigation. The communication of this information must be documented as an update to the ICF and re-consent of the subject.

11 ADVERSE EVENTS AND DEVICE DEFICIENCIES

Not applicable.

12 DEVICE ACCOUNTABILITY

Not applicable.

13 DEVIATIONS FROM THE CLINICAL INVESTIGATION PLAN

The Investigator(s) must not deviate from the CIP, except in case of an emergency to protect the safety and well-being of the subject(s). Such deviations will be documented by the site personnel in the source documentation for the subject and reported to the relevant EC as per institutional requirements and to the Sponsor as soon as possible.

If there is a deviation from CIP-defined assessments or parts thereof are omitted or completed incorrectly, the deviation will also be documented by the site personnel in the source documentation for the subject. Depending on the type or severity of the deviation the Investigator may be required to notify the EC, particularly if the deviation potentially impacts subject safety or data integrity.

All CIP deviations will be documented in the eCRF to enable analysis and reporting by the Sponsor in the Clinical Investigation Report (CIR), or to the relevant regulatory authority(s), if applicable.

Gross misconduct on behalf of an Investigator, such as intentional non-compliance with CIP or GCP requirements or fraud, will result in disqualification of the Principal Investigator and/or Investigational Site from participation in the investigation. Data provided by the Principal Investigator or Investigational Site will be excluded from the per-protocol analysis group.

14 DATA MANAGEMENT

The CRF will capture the datapoints necessary to determine the subject status according to the criteria described in section 7.2.5.

Source data can be medical records, paper-based source data worksheets, questionnaires and survey. If electronic medical records do not permit read only access for monitoring purposes or an authorized site member is not available to ensure access to the electronic medical records, a certified printout must be provided.

Data collection will be performed using Medidata Rave for electronic data capture (EDC) on electronic Case Report Forms (eCRFs). Site staff will be trained on the completion of the eCRFs prior to obtaining access to the system and will have their own Login/Password. Access to clinical study information will be based on an individual's role and responsibilities.

Medidata Rave uses role-based user permissions for data entry, viewing, and reporting options. All communications between users and the EDC server are encrypted. Web servers are protected by a managed firewall. This application is designed to be in compliance with applicable regulations including 21 CFR Part 11.

The application will include programmed data consistency checks and supports manual generation of data clarifications/queries, including documentation of site responses. The application maintains a

comprehensive audit trail for all data entered, including updates and queries, and it documents the time that each entry occurred and who made the entry.

Principal Investigators will affirm that the data for each subject at their site is accurate and complete by way of an electronic signature.

15 CONFIDENTIALITY

The investigator, site staff and the Sponsor will collect and process personal data of the subjects in accordance with governing data privacy regulations [such as the EU GDPR regulations]. Subjects have the right to access their data and request for its correction or deletion after withdrawal.

Data will be reported to the Sponsor on CRFs or related documents (for example, questionnaires). Subjects will be identified on CRFs and other related documents only by a unique subject identification code and shall not include the subject's name or other personal identifiable information. Completed CRFs or related documents are confidential and will only be available to the Investigator and site staff, the Sponsor and their representatives, and if requested to the Ethics Committee and national regulatory authorities. Publications or submission to a regulatory authority shall not disclose the identity of any subject.

16 ETHICS COMMITTEE AND REGULATORY AUTHORITY APPROVAL

The clinical investigation will not commence prior to the written favourable opinion or approval from the EC and/or regulatory authority (if appropriate) is obtained.

The final Sponsor-approved version of the CIP, Informed Consent Form and other necessary documents shall be submitted to the EC. A copy of the EC opinion/approval shall be provided to the Sponsor.

The Investigator shall forward to the Sponsor, for review and approval, any amendment made to the approved ICF and any other written information to be provided to the subject prior to submission to the EC.

The Sponsor and Principal Investigator will continue communications with the EC, as required by national regulations, the clinical investigational plan, or the responsible regulatory authority.

Any additional requirements imposed by the EC or regulatory authority will be implemented by the Sponsor.

The Investigator shall submit the appropriate documentation if any extension or renewal of the EC approval is required. In particular, substantial amendments to the CIP, the ICF, or other written information provided to subjects will be approved in writing by the EC.

The Investigator shall report to the EC any new information that may affect the safety of the subjects or the conduct of the clinical investigation. The Investigator will send written status summaries of the investigation to the EC regularly, as per local EC requirements.

Upon completion of the clinical investigation, the Investigator shall provide the EC with a brief report of the outcome of the clinical investigation, as per local EC requirements.

The clinical investigation is covered by clinical trial insurance, meeting the requirements of the participating countries.

17 Suspension or Premature Termination

The Sponsor will discontinue the clinical investigation site if:

1) major non-adherence to the CIP or GCP principles is occurring
2) it is anticipated that the subject recruitment will not be adequate to meet the objectives of the clinical investigation

18 Amendments to the Clinical Investigation Plan

No changes in the CIP or investigation procedures shall be made without mutual agreement of the Coordinating Investigator and the Sponsor. This agreement will be documented as a CIP amendment. Amendments will require notification to the Ethics Committees (ECs) by the Principal Investigators.

19 Record Keeping and Retention

Data generated from the clinical investigation will be stored in a limited-access file area and be accessible only to representatives of the study site, the Sponsor and its representatives, and relevant health authorities/regulatory agencies. All reports and communications relating to study subjects will identify subjects only by subject unique identification code. Complete subject identification will be maintained by the Investigator. This information will be treated with strict adherence to professional standards of confidentiality.

The investigator must retain study-related records in accordance with the period required by local regulation, as follows:

Country	Retention period
Germany	At least 15 years
France	At least 15 years
Spain	At least 5 years

The Sponsor will notify the Principal Investigator when records are no longer needed. The Investigator will not discard any records without notifying the Sponsor. If the Principal Investigator moves from the current investigational site, the Sponsor should be notified of the name of the person who will assume responsibility for maintenance of the records at the investigational site or the new address at which the records will be stored. The Investigator will notify the Sponsor as soon as possible in the event of accidental loss or destruction of any study documentation.

20 Publication Policy

This clinical investigation will be prospectively registered at a public clinical trial registry (ClinicalTrials.gov).

A joint peer-reviewed publication authored by the clinical investigator(s) and Sponsor will be prepared. In addition, the results of the clinical investigation may also be disseminated as conference presentations (for example, abstract and poster session). Manuscript authorship and responsibilities

will be discussed and agreed upon prior to investigation start and in accordance with guidelines and recommendations provided by the International Committee of Medical Journal Editors (ICMJE) to enable communication in a timely manner. All contributors who do not meet the criteria for authorship will be listed in an acknowledgments section of the publication.

Investigators will also be able to publish and/or present the data generated from the clinical investigation after mutual agreement between the Coordinating Investigator, the Principal Investigators, and the Sponsor when the main publication has been submitted and approved.

21 STATEMENTS OF COMPLIANCE

This clinical investigation shall be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki, International Standard ISO 14155 Clinical investigation of medical devices for human subjects - Good Clinical Practice, and any regional or national regulations, as applicable.

22 QUALITY CONTROL AND ASSURANCE

In accordance with Cochlear's Quality Management System, all clinical investigations shall be conducted according to internationally recognised ethical principles for the purposes of obtaining clinical safety and performance data about medical devices.

The Sponsor employees (or designee) shall use standard operating procedures (SOP) to ensure that clinical investigation procedures and documentation are consistently conducted and compliant with the ISO 14155 Standard, Good Clinical Practice (GCP), and applicable local regulations.

22.1 Monitoring

The Sponsor will perform on-site and remote monitoring visits as frequently as necessary to oversee conduct, data collection and record keeping by sites. The clinical investigation monitoring plan is a separate document describing all the activities performed during site qualification, initiation, monitoring, and close out.

22.2 Audits

An Investigator must, in reasonable time, upon request from a relevant health authority or regulatory agency, permit access to requested records and reports, and copy and verify any records or reports made by the Investigator. Upon notification of a visit by a regulatory authority, the Investigator will contact the Sponsor immediately.

The Investigator will grant the Sponsor representatives the same access privileges offered to relevant health authority or regulatory agents, officers, and employees.

23 TRADEMARKS AND COPYRIGHT

Not applicable.

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25 CHANGE HISTORY

Version	Change	Rationale
1.0	Initial version of document	NA
2.0	• Exclusion criteria on subjects with other chronic diseases removed. • French specific items removed and added to a country-specific CIP. • More details added on the number of subjects to be recruited and distribution per clinic. • More clarification on the sample size calculation. • More details added to the exploratory endpoints and its analysis. • Corrected order of exploratory objectives in section §6.3 to reflect ordering used in rest of document. • Added Investigator at Stage 2 in section §3	Changes done in reply to comments from French Ethics Committee.

Version	Change	Rationale
3.0	• Estimated recruitment period updated to reflect current plan. • Clarification added if any site has difficulties with recruitment, the remaining sites are allowed to include more subjects than the even distribution initially planned, upon agreement with Sponsor. • Upper limit of participating investigational sites increased from 6 to 9. • Changes to the inclusion criteria: - Time window of primary tympanoplasty changed from 2015 to 2016. - Hearing loss inclusion criteria on PTA4 air-bone gap ≥30 dB extended to cover patients with a PTA4 air-bone gap between 25-30 dB together with an air conduction threshold PTA4 ≥40 dB HL". - Time window for post-op audiogram in hearing loss inclusion criteria extended to 12 months. - Hearing aid inclusion criteria changed from have "tried a hearing aid" to have "been recommended by their health care professional to try a hearing aid". • Monitoring services outsourced to Clinical Research Organisation (CRO) extended to French sites.	Changes done to reflect impact of COVID and administrative delays on the timeline and also to support recruitment efforts by increasing the pool of eligible subjects that represent the current standard of care in the participating countries and by allowing other sites to recruit more subjects if a specific one is having difficulties doing so. CRO monitoring services extended to French sites due to changes of internal resources.
4.0	• Change of Coordinating Investigator from [redacted] • Inclusion criteria #8 changed to allow latest audiogram to be from 2018 to point of enrolment. • Clarification added on data that is to be collected from Medical Records. • Surgical data supporting exploratory objective to be collected only if available. • Estimated recruitment period adapted to reflect current expectations. • Cost year adapted to 2022 instead of 2021.	Origin of change was the switch of Coordinating Investigator. Opportunity was taken to adapt the inclusion criteria #8 to allow subjects that have not had a follow-up audiogram in the last 12 months pre-enrolment (impact from COVID) to take part in the study; Clarification on data to be collected (including the change made to surgical data collection requirements) added to avoid protocol deviations, based on experience so far.

APPENDIX 1: INFORMATION COLLECTED FROM MEDICAL RECORDS

Demographics
Date of written Informed consent
Sex
Date of Birth
Risk factors
Hearing History (BAS)
Hearing Loss
Age at onset of Hearing Loss
Hearing loss type
History of hearing loss
Primary case of hearing loss
Diagnosis of COM
Age at onset of COM
Device Exposure
Ear
Device type (implant, sound processor, HA)
Device name
Implantation and Explant Date (if applicable)
Device use start date
Device use end date
Device History – Hearing Aid (HA)
Has the subject used a HA?
Age initial HA used
Most recent HA type
HA use
Reason for intermittent use
If applicable, when did patient stop using HA?
Primary reason HA no longer used
Concomitant Medications and Therapies – COM-related only for the operated ear
Medication taken / therapies
Why was medication / therapy prescribed
Referent Ear
Start Date
End date
Dose and unit
Frequency
Route of administration
Audiogram (BAS) – For Pre- and post-primary tympanoplasty and latest available audiogram only for the operated ear
Date
Presentation Mode (AC, BC)
Aided or Unaided
Masked/Unmasked
Device details
250 Hz - 8K Hz
Result Qualifier
Health Care Contacts – COM-related only for the operated ear
Type of contact

Reason for contact/procedure
DRG Code
Start date
End date
Care provider
Inpatient days
Ear

Medical Examinations – COM-related only for the operated ear

Exam or Procedure
Date
Code of action/procedure
Ear

Preoperative Status – if available

Side of operation
Symptoms
Middle Ear status
Contralateral ear
Presence of extracranial complications
Presence of intracranial complications

Surgical Procedure – if available

Date of surgery
Stage
Approach
Mastoidectomy procedure
External Canal Reconstruction Category
External Canal Reconstruction materials
Obliteration Category
Obliteration Flap
Obliteration material
Access to middle ear
Type of tympanic membrane Repair performed
TM graft materials
Position of TM graft
Ossicular defect at time of reconstruction
Ossiculoplasty Category
Ossiculoplasty material
Stapes Surgery Category
Stapes Surgery prosthesis
Ossicular prosthesis

Intraoperative Findings – if available

Cholesteatoma
Extent of cholesteatoma
Type of cholesteatoma
Retraction pocket
Retraction pocket location
Mobility of retraction pocket
Perforation size
Perforation location
Ossicular Erosion

Ossicle eroded
Ossicle fixed
Middle ear mucosa
Active discharge
Presence of Middle Ear Effusion
Facial Nerve
Fistula
Fistula with labyrinth disturbance
Canal Wall destruction
Tegmen destruction that require repair
Brain herniation into mastoid cavity

Surgical Outcomes – if available

Date of assessment
Complications
Otorrhoea
Otoscopic appearance
Cholesteatoma
Ossicular prosthesis dislocation
Ossicle head or stapes fixation
Tympanic membrane perforation
Granulation

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