# Feasibility of structural and functional imaging of the middle ear and its constituents by optical coherence tomography

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|---|---|
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| **Subsidising party** | |
| **Independent expert (s)** | ***n/a (cf Article 4(1) WMO)*** |

**PROTOCOL SIGNATURE SHEET**

| Name | Signature | Date |
|---|---|---|
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## LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

| | |
|---|---|
| **AE** | **Adverse Event** |
| **CCMO** | **Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek** |
| **CT** | **Computed Tomography** |
| **CV** | **Curriculum Vitae** |
| **DSMB** | **Data Safety Monitoring Board** |
| **EU** | **European Union** |
| **EudraCT** | **European drug regulatory affairs Clinical Trials** |
| **GCP** | **Good Clinical Practice** |
| **IB** | **Investigator's Brochure** |
| **IC** | **Informed Consent** |
| **METC** | **Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)** |
| **MRI** | **Magnetic Resonance Imaging** |
| **OCT** | **Optical Coherence Tomography** |
| **OM** | **Otitis Media** |
| **(S)AE** | **(Serious) Adverse Event** |
| **Sponsor** | **The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.** |
| **SUSAR** | **Suspected Unexpected Serious Adverse Reaction** |
| **TM** | **Tympanic membrane** |
| **WMO** | **Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen** |

**SUMMARY**

**Rationale:** Various middle ear diseases can affect anatomical structures of the middle ear in different ways. Unfortunately, current methods for assessing the structure and function of the constituents of the middle ear are limited and often fail to provide all clinically relevant data. Optical coherence tomography (OCT) is a technology that can provide valuable, additional information. Aurisvue is a newly developed prototype OCT-device for structural and functional imaging of the middle ear.

**Objective**: To assess the feasibility and the clinical potential of structural and functional OCT imaging with Aurisvue in patients with various middle ear problems.

**Study design:** Observational study

**Study population:** Adult patients presenting with various middle ear complaints at the ENT-department of the Department of Otorhinolaryngology and Head and Neck Surgery, Erasmus Medical Center, Rotterdam, the Netherlands.

**Main study parameters/endpoints:** Percentage of patients in which structural OCT imaging was feasible (i.e., the OCT images showed a discernible tympanic membrane (TM) and at least one of the ossicles).

**Nature and extent of the burden and risks associated with participation, benefit and group relatedness:** The burden is minimal: patient examination with Aurisvue is similar to the conventional examination with a standard otoscope and will take approximately 5 to 10 minutes. The risks are negligible: imaging is done with light levels well below the maximum permissible exposure level and sound levels to induce movement of the TM and the ossicular chain are well below the hazardous threshold.

## 1. INTRODUCTION AND RATIONALE

The middle ear is an anatomical part of the auditory system that consists of the tympanic membrane (TM), the tympanic cavity and the ossicles. The physical function of the middle ear is to adapt the air-pressure waves to the inner ear's fluid-filled cavity. Acoustic pressure waves are captured by the tympanic membrane and subsequently transferred by the malleus, the incus and the stapes. The footplate of the stapes is located in the oval window, resulting in vibration of the perilymph in the inner ear. The hair cells in the inner ear convert these vibrations into electrical impulses that are transmitted into the central nervous system. The normal middle ear contains air with normobaric pressure.

In patients with otitis media (OM), either acute or chronic, the tympanic cavity is filled with fluid. When this is due to an infection of the upper airway, the patient suffers from acute otitis media. Acute OM is very common, with an incidence rate of almost 11% and more than half of these occurring in children under 5 years old[1]. Fluid may accumulate in the middle ear, followed by bacteria and viruses, resulting in the formation of biofilm and in middle ear inflammation. The increased pressure in the middle ear cavity leads to bulging of the TM and may lead to typical symptoms such as pain and fever and common complications are TM rupture and hearing loss (prevalence of 31 per 10.000[1]). The chronic type of OM is not a result of a classic bacterial or viral infection, but appears to result from problematic aeration of the tympanic cavity. This can be due to Eustachian tube dysfunction and/or hampered ventilation of the middle ear mucosa. Treatment options of OM include observation, medication to reduce the symptoms, antibiotic therapy or surgical placement of tympanostomy tubes[2].

A special type of OM is cholesteatoma. In this condition, the skin of the tympanic membrane grows into the middle ear cavity and the mastoid leading to erosion and finally destruction of bony structures including the ossicles and the mastoid, the facial nerve and the semicircular canals (vestibular system). Patients usually suffer from a chronically discharging ear, hearing loss and sometimes vertigo.

Hearing loss related to the middle ear can be due to perforation or retraction of the tympanic membrane, middle ear effusion, erosion or dislocation of the ossicles and ankylosis of the stapes (otosclerosis). All these conditions can cause a conductive hearing loss. To determine the cause of this type of hearing loss, otoscopy is the first diagnostic procedure. This is performed with a hand-held otoscope or with a binocular microscope. Because the tympanic cavity is sealed by the TM which is partially transparent, visualization of the middle ear structures is not as straightforward. Computed tomography (CT) and magnetic resonance imaging (MRI) are the most common imaging modalities for imaging middle ear pathology[3]. High-resolution CT scanning can be used to visualize the middle ear including the ossicles

and the inner ear, but very small structures like the stapes arch can be difficult to identify. Differentiation of cholesteatoma from other types of tissue and from fluid is difficult with CT. Moreover, CT involves radiation exposure. MRI is used in special cases when soft tissue structures need to be visualized. These are the internal auditory canal, fluid in the cochlea and labyrinth and cholesteatoma. Currently, there is no functional imaging modality available to identify the location of reduced transduction of vibration in case of conductive hearing loss. Therefore, the ossicular chain is often best inspected during surgery. The availability of an imaging technology that is able to identify middle ear structures in high resolution and assess the transduction of acoustic vibrations by the ossicular chain, might reduce the burden on the patient, provide additional insight to the clinician to more accurately diagnose the cause of conductive hearing loss, improve surgical planning and evaluate the result of a reconstructive procedure.

Optical coherence tomography (OCT) is an interferometric imaging modality that produces depth-resolved images of semi-transparent media[4]. It was first developed for ophthalmology and is routinely used in clinical practice for over a decade. It enables volumetric, high-resolution imaging of, for example, the chorioretinal complex, where many different layers can be visualized. Similar to ultrasound, Doppler-OCT, an extension to OCT, can also be used to measure motion, e.g., blood flow[5]. Due to the semi-transparent nature of the TM, OCT may also be used for imaging of the middle ear to identify the TM, any fluid behind the TM and the ossicular chain (see Figure 1). Doppler-OCT can be used to measure the vibrations of the various components of the auditory system (i.e., the TM and the ossicles; OCT-vibrometry, see Figure 2)[6].

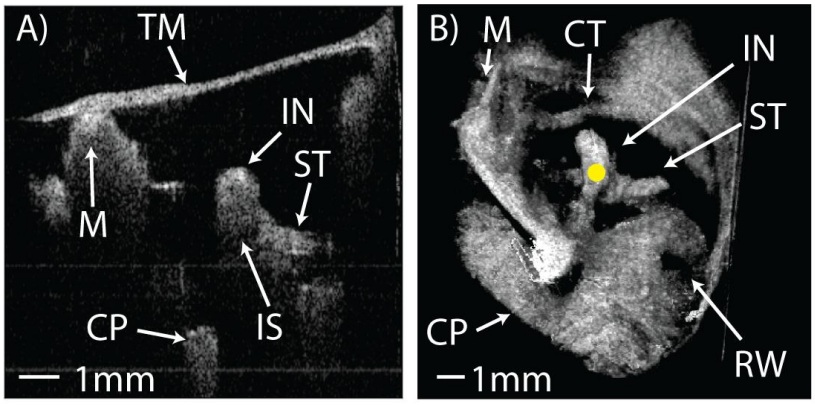


Figure 1. In vivo OCT imaging of a normal subject's left ear. A) Shows a 1×1cm$^2$ 2D cross-section of the middle ear in the transverse plane. B) Shows a 1×1×1cm$^3$ 3D volume render of the middle ear as seen from the perspective of the ear canal with the TM digitally removed. Tympanic membrane (TM), malleus (M), incus (IN), incudo-stapedial joint (IS), stapedius tendon (ST), chorda tympani nerve (CT), cochlear promontory (CP), round-window niche (RW).[7]

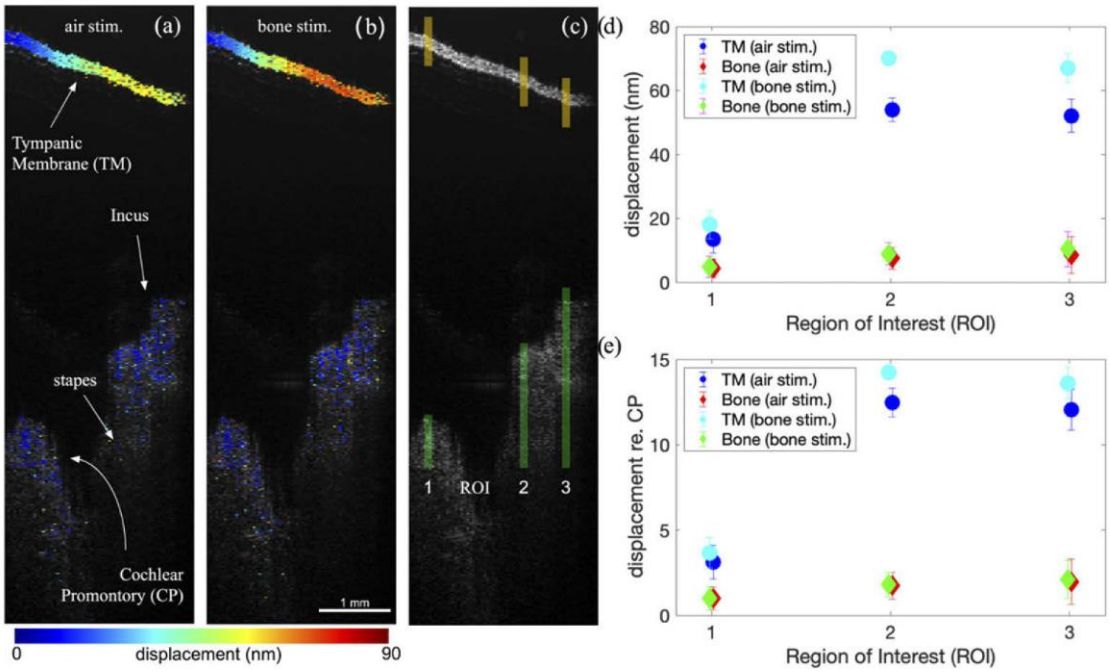


Figure 2. (a)-(b) Overlay of vibratory response (color scale) on the morphological image (gray scale) of the middle ear. (a) Pure tone stimulus was at 800 Hz and 70 dB SPL. (b) Bone stimulus calibrated to give similar vibratory response at the cochlear promontory. (c) Morphological image showing the 3 regions of interest (ROI) used to generate the plots in (d) and (e). (d) Plot of the displacement for the ROI at the TM and bone (Cochlear Promontory or Incus) resulting from air and bone stimulation. (e) Displacement data from (d) plotted relative to the vibratory response at the cochlear promontory.[8]

Preliminary results from many different prototype research instruments have been published, primarily focused on imaging of the TM and any adjacent fluid, although other diseases were also explored[9–12]. Despite the heterogeneous set of devices, methodologies and diseases, the results indicate that application of OCT in otology is promising and could provide clinically relevant information that is currently not available.

To the best of our knowledge, no systems have been approved in the EU for clinical use in otology. Aurisvue CIM is a novel, handheld, clinical prototype OCT device, developed by Acoustic Insight. It features both structural OCT imaging and functional OCT imaging (OCT-vibrometry) and is specifically designed for middle ear imaging. In this study, we aim to identify clinically relevant applications of Aurisvue for middle ear imaging. Based on the results from this study, Aurisvue will be further developed for specific clinical applications and evaluated in future trials.

## 2. OBJECTIVES

Primary Objective:

- To assess the feasibility of structural OCT imaging with Aurisvue in clinically relevant subjects with middle ear problems.

Secondary Objectives:

- To assess the feasibility of functional OCT imaging with Aurisvue in clinically relevant subjects with middle ear problems.
- To assess the clinical potential of structural and functional OCT imaging with Aurisvue in clinically relevant subjects with middle ear problems.

## 3. STUDY DESIGN

This study is an observational study. No treatment intervention for study purposes is included and all patients will receive routine clinical care. The study is intended to explore the feasibility and possibilities of OCT for structural and functional imaging of the middle ear.

The duration of the study will be approximately one year. Patients will be recruited from those visiting the Department of Otorhinolaryngology and Head and Neck Surgery, Erasmus Medical Center, Rotterdam, the Netherlands.

Patients included in the study will be imaged at least once with Aurisvue. If a patient returns to the site within the duration of the study and relevant physiological or pathological changes to the middle ear are expected (due to, for example, treatment or the natural history of the disease), the patient may be imaged again. Except for assessment with Aurisvue, no study related procedures are prescribed, and patients will receive the usual standard of care.

# 4. STUDY POPULATION

## 4.1 Population (base)

Approximately 100 patients will be recruited from those visiting the ENT-department with various middle ear problems, as assessed by the otolaryngologist. Because a heterogenous study population is needed to evaluate a wide range of abnormalities of the middle ear, patients will be stratified according to the table below.

| condition | Max. number of patients |
|---|---|
| chronic suppurative otitis media | 10 |
| conductive hearing loss of unknown origin | 20 |
| conductive hearing loss after head trauma | 10 |
| cholesteatoma | 10 |
| perforated tympanic membrane | 10 |
| total middle ear prosthesis TORP in situ | 10 |
| partial middle ear prosthesis PORP in situ | 10 |
| interpositioned incus in situ | 10 |
| cochlear implant in situ | 10 |
| previous tympanoplasty | 10 |
| glomus tumor in middle ear (glomus tympanicum) | 10 |
| sclerosis of the tympanic membrane (myringosclerosis) | 10 |

## 4.2 Inclusion criteria

In order to be eligible to participate in this study, a patient must meet all of the following criteria:

- age 18 or older,
- competent, willing and able to cooperate.

## 4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study in case of:

- any acute or chronic condition that would limit the ability of the patient to participate in the study, per attending physician’s indication, including:
    - abnormally narrow or stenotic external ear canal,

  - external otitis,
  - significant exostosis of the ear canal,
  - radical cavity,
  - movement disorder causing inability to keep head still during imaging.
- refusal to give informed consent
- pregnancy or breastfeeding

### 4.4 Sample size calculation

Due to the exploratory nature of this study, no formal sample size calculation can be performed. The study aims to include patients with various middle ear problems (disease). For each specific disease, not more than the specified maximum number of patients will be included. The total number of included patient will not exceed 100.

## 5. TREATMENT OF SUBJECTS

Not applicable as this is not an intervention study.

# 6. INVESTIGATIONAL PRODUCT

## 6.1 Name and description of investigational product(s)

Product name: Aurisvue CIM
Aurisvue is an optical coherence tomography (OCT) system designed specifically for assessing the structure and function of the middle ear.
For further details, please refer to chapter 1 (section 2.1) of the IMDD.

## 6.2 Summary of findings from non-clinical studies

Not applicable because sufficient data is available from clinical studies to assess the basic safety and potential applicability of the technology.

## 6.3 Summary of findings from clinical studies

Please refer to chapter 6, section 2 of the IMDD.

## 6.4 Summary of known and potential risks and benefits

Please refer to chapter 5 of the IMDD.

## 6.5 Description and justification of route of administration and dosage

Not applicable.

## 6.6 Dosages, dosage modifications and method of administration

Not applicable.

## 6.7 Preparation and labelling of Investigational Medicinal Product

Not applicable.

## 6.8 Drug accountability

Not applicable.

## 7. NON-INVESTIGATIONAL PRODUCT

Not applicable, the study does not concern any non-investigational products.

# 8. METHODS

## 8.1 Study parameters/endpoints

### 8.1.1 Main study parameter/endpoint

Presence of a discernible TM and the number of discernible ossicles on structural OCT imaging.

### 8.1.2 Secondary study parameters/endpoints (if applicable)

- Number of middle ear structures (TM, ossicles) on which OCT-vibrometry measurements by Aurisvue succeeded.
- For diagnostic correlation with other clinical data sources (only as far as they are available from the standard of care):
    - microscopic otoscopy (description)
    - CT-scan
    - MRI-scan
    - pure-tone audiogram
    - tympanogram
    - surgical report (if available)
- Number of AEs and SAEs
- PREMs

### 8.1.3 Other study parameters (if applicable)

- Demographic characteristics
- Clinical diagnosis of middle ear disease
- Description of relevant interventions before or during study period (if applicable)

## 8.2 Randomisation, blinding and treatment allocation

Not applicable.

## 8.3 Study procedures

<u>Discernible TM and discernible ossicles on structural OCT imaging.</u>

OCT images acquisition by Aurisvue will be performed on both ears of every patient. The acquisition process consists of positioning the Aurisvue's handheld interface in the ear canal of the patient and collecting data during a period of a few minutes. Several two- or three-dimensional scans may be acquired during this time, each focusing on regions of interest in the middle ear. During acquisition, the OCT images are displayed on the monitor of the

computer to guide the operator. Data may be processed at a later stage to improve image quality. The processed images will be evaluated by a medical specialist to identify the anatomic features. Visibility of the TM and of the ossicles will be registered as outcomes (primary endpoint).

Number of middle ear structures (TM, ossicles) on which OCT-vibrometry measurements by Aurisvue succeeded.

The assessment procedure for OCT-vibrometry is similar to the structural imaging described above. In OCT-vibrometry mode, Aurisvue will produce a sound stimulus and will subsequently measure differences between repeated scans. Vibrometry is successful if the signal on the region of interest is sufficient to determine the amplitude of the vibration that matches the characteristics of the stimulus.

Diagnostic correlation with other clinical data sources from the standard of care.

Procedures/assessments may include:

- microscopic otoscopy (description)
- CT scan
- MRI scan
- pure-tone audiogram
- tympanogram
- surgical report (if available)

These procedures/assessments will all follow the standard of care at the clinical site. Both the results of the assessments and the interpretation thereof by the clinician will be used to evaluate the diagnostic correlation with structural and functional imaging results by Aurisvue.

PREMs (for subjects).

Patients will be asked about their experience with otoscopy with Aurisvue compared to regular or microscopic otoscopy (one question).

Number of AEs and SAEs

These will be reported as detailed in section 9 (Safety reporting).

### 8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

### 8.4.1 Specific criteria for withdrawal (if applicable)

Not applicable.

## 8.5 Replacement of individual subjects after withdrawal

Subjects will only be replaced in case the first visit (i.e., the first, full assessment procedure with Aurisvue) was not completed for purposes that were unrelated to the performance or the characteristics of Aurisvue.

## 8.6 Follow-up of subjects withdrawn from treatment

Not applicable.

## 8.7 Premature termination of the study

The study will be terminated in case the performance of the device is insufficient to warrant further inclusion or follow-up of study subjects or if regulatory requirements are no longer met (e.g., if the manufacturer cannot support the study any longer because it stops pursuing the use of OCT technology for middle ear problems).

# 9. SAFETY REPORTING

## 9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise the patient's health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

## 9.2 AEs, SAEs and SUSARs

### 9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational medical device. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will reported by the investigator to the Sponsor by filling out the corresponding eCRF. The Sponsor will record all AEs, based on NCI CTCAE reporting standards[13].

### 9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death,
- is life-threatening (at the time of the event),
- requires hospitalisation or prolongation of existing inpatients' hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator

An elective hospital admission will not be considered as a serious adverse event.

The investigator will report all SAEs that may be related to the Aurisvue device or Aurisvue operating procedures to the sponsor and the manufacturer without undue delay after obtaining knowledge of the events, except for the following SAEs: None

The sponsor will report these SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in

death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

### 9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable (no investigational medicinal product).

## 9.3 Annual safety report

Not applicable (no investigational medicinal product).

## 9.4 Follow-up of adverse events

All AEs will be followed until they have abated or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

## 9.5 Data Safety Monitoring Board (DSMB) / Safety Committee

Not applicable.

# 10. STATISTICAL ANALYSIS

## 10.1 Primary study parameter(s)

The presence of a discernible TM and the number of discernible ossicles on structural OCT imaging will be reported by descriptive statistics. This will be the primary source of information for the primary objective of this study: To assess the feasibility of structural OCT imaging with Aurisvue in clinically relevant subjects with middle ear problems.
Because the occurrence of missing data (e.g., no OCT was acquired) is of interest for the primary objective of this study, no imputation will be performed. Instead, missing data will be reported as such, including the reasons of such missing data.

## 10.2 Secondary study parameter(s)

Answering the first secondary objective (‘To assess the feasibility of functional OCT imaging with Aurisvue in clinically relevant subjects with middle ear problems’) will be done in the same way as described above for the primary objective, albeit based on functional OCT-vibrometry measurements using a sound stimulus rather than the structural OCT images.
For the second secondary objective (‘To assess the clinical potential of structural and functional OCT imaging with Aurisvue in clinically relevant subjects with middle ear problems’), the data obtained by Aurisvue will be (qualitatively) correlated with other clinical data sources. Similarities such as Aurisvue image information consistent with other imaging modalities) and dissimilarities (such as characteristics visible on Aurisvue images but not on another imaging modality) will be evaluated.
AEs, SAEs and questionnaires will be included in answering the primary and both secondary objectives. Again, missing data will be reported and not imputed.
Patient reported experience measures (PREMs) will be recorded immediately after the measurements with Aurisvue are completed.

## 10.3 Other study parameters

All other study parameters may be used to stratify the data used to answer the primary and secondary objectives. Again, because no power calculation was performed, no definite conclusions may be drawn from this analysis, but it may be used to produce new hypotheses for future testing.

## 10.4 Interim analysis (if applicable)

Not applicable.

# 11. ETHICAL CONSIDERATIONS

## 11.1 Regulation statement

This study will be conducted in accordance with the principles of the Declaration of Helsinki (October, 2013), the Medical Research Involving Human Subjects Act (WMO; July 1, 2021), the Guidelines for Good Clinical Practice E6(R2) (EMA/CHMP/ICH/135/1995, Dec 1, 2016) and the EU Medical Device Regulations (2017/745).

## 11.2 Recruitment and consent

Patients scheduled for a visit at the ENT-department will be screened based on the available information (medical records and/or referral information). Prospective participants will be informed by the otolaryngologist at their visit and are provided with additional information by letter (brochure) that they take home. The researcher contacts the participant at least 2 days later by phone and, when the patient decides to participate, schedules the appointment for a research visit. During the research visit, any questions regarding the study can be answered and the participant will be asked to provide written informed consent for the study. Costs for travelling and parking will be reimbursed.

## 11.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable.

## 11.4 Benefits and risks assessment, group relatedness

Subjects do not benefit from participation. The risk is minimal (see chapter 5 of the IMDD for the full risk assessment and benefit-risk analysis). The burden of participation is low: the assessment with Aurisvue is expected to take approximately 10 minutes of extra time during a study visit.

## 11.5 Compensation for injury

The sponsor and investigator have a liability insurance which is in accordance with article 7 of the WMO.
The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

In addition, the manufacturer of the Aurisvue has a product liability insurance that covers the product liability of the non-CE-marked Aurisvue within the scope of this clinical investigation.

### 11.6 Incentives (if applicable)

Not applicable.

# 12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

## 12.1 Handling and storage of data and documents

Access to patient information is restricted to members of the study team and to legitimate authorities only. No identifiable data on participants will be stored within the context of this study, except for the informed consent forms and the enrolment log. All data will be pseudonymized: data will be encoded by a patient code that is specific for this study and is unrelated to the clinical patient ID. The key to the patient code is available only to the investigator and the site's study team. All data will be stripped from identifiable information by the site prior to submitting such data to the study systems.
All data will be entered into an electronic data capture system (Castor EDC). Larger data points, such as large (three-dimensional) images or videos, will be pseudonymized and uploaded in the same system.
Processing of the data and presentation of the results of this study will be strictly anonymous. An export of the data stored in the EDC system will be shared with Acoustic Insight, the manufacturer of the Aurisvue, according to the provisions of the collaboration agreement and as specified in the patient information file.

## 12.2 Monitoring and Quality Assurance

Based on the NFU risk table (see Annex 2 of NFU Richtlijn Kwaliteitsborging Mensgebonden Onderzoek, December 2020), the following risks were estimated:

| | |
|---|---|
| For patients: | Negligible |
| For research data: | Negligible |
| Overall: | Negligible |

Monitoring will be done by personnel that is not part of the Investigator's study team and will be performed in accordance with Annex 3 of the beforementioned NFU Guideline (column 'Verwaarloosbaar risico: Geneesmiddelen-, Medische hulpmiddelenen Voedingsonderzoek').

## 12.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

## 12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject,

numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

### 12.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

### 12.6 Public disclosure and publication policy

Relevant results of this study will be submitted for presentation at scientific meetings and/or for publication in a scientific journal. Authorship of any scientific publication and/or public disclosure will be in accordance with the guidelines of the International Committee of Medical Journal Editors (ICMJE).

## 13. STRUCTURED RISK ANALYSIS

Please refer to chapter 5 of the IMDD for more details on the risk analysis. Here, the items that are specifically of interest for patient safety are listed.

### 13.1 Potential issues of concern

a. Level of knowledge about mechanism of action

OCT is based on the fundamentals of interferometry, which were established in the 19th century. OCT itself has been studied intensively since its inception in the early 90's. Different variations have been developed as well, including Doppler or phase-sensitive OCT, polarization-sensitive OCT and OCT-vibrometry. These have all been extensively evaluated theoretically and practically.

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

OCT is a well-established clinical imaging modality in ophthalmology[14], including pediatric ophthalmology[15]. It is also used in various other medical applications, such as dermatology[16], gastroenterology[17], urology[18], dentistry[19] and for intravascular imaging[20]. OCT uses near infrared light to probe the tissue with intensities that are well below the maximum permissible exposure of light.

Aurisvue employs this well-known OCT technology for the application of structural and functional imaging of the middle ear. No OCT-device for imaging of the middle ear is currently approved for use in the EU. However, PhotoniCare's Otosight has been approved for clinical use by the FDA and clinical trials with both Otosight and Ossiview (Audioptics Medical Inc, USA) are registered (NCT03890107, NCT04722770, NCT05085379). Both devices use OCT technology that is similar to Aurisvue.

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?

OCT has been demonstrated in animals and ex-vivo human tissue.

d. Selectivity of the mechanism to target tissue in animals and/or human beings

OCT is primarily used to image semi-transparent tissue. Media without scattering of the light (e.g., air, water) are not resolved on OCT. Fully opaque media block the light of the OCT beam and prevent imaging at larger depths. The tissues of interest in the middle ear are semi-transparent.

e. Analysis of potential effect

N/a. There is no treatment intervention. Harmful effects from OCT imaging are not expected since the light levels used are below the maximum permissible exposure levels.

f. Pharmacokinetic considerations

Not applicable.

g. Study population

No increased risks are expected due to the specific characteristics of the study population.

h. Interaction with other products

Not applicable.

i. Predictability of effect

Not applicable.

j. Can effects be managed?

Not applicable.

### 13.2 Synthesis

There are three main potential sources of risk for patients: optical power, acoustical power and malfunction of the integrated camera.

- The intensity of the OCT beam is below the maximum permissible exposure level for continuous illumination of tissue. Aurisvue employs two scanners for lateral imaging. Typical imaging duration is a few minutes. The probability of harm due to optical power is therefore improbable. The severity of the harm is moderate (CTCAE grade 2). The risk related to optical power is deemed to be insignificant (and thus acceptable).
- Likewise, the sound used to induce movement of the TM and ossicular chain for OCT-V measurements is well below the hazardous threshold, even when used continuously. The probability of harm directly due to acoustic power is therefore improbable. The severity of this harm is moderate (CTCAE grade 2). This risk directly related to acoustic power is deemed to be insignificant (and thus acceptable).

  In addition, there is an indirect risk related to unexpected exposure to an acoustical stimulus, which may cause a patient to suddenly move his head. The probability of harm due to sudden movement of the patient's head caused by unexpected acoustical exposure is improbable. The severity of this harm is severe (CTCAE grade 3). The risk

related to this sudden movement is deemed to be acceptable. It is addressed in the Aurisvue's instructions for use and will be addressed during training.

- Malfunctioning of the integrated camera limits the feedback to the operator with respect to the location of the device and may therefore result in inadvertent contact of the speculum with the tympanic membrane. The probability of harm due to a malfunctioning camera is improbable. The severity of this harm is severe (CTCAE grade 3). The risk related to a malfunctioning camera is deemed to be acceptable. It is addressed in the Aurisvue's instructions for use and will be addressed during training.

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