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CLINICAL INVESTIGATION PLAN (CIP)

Clinical Investigation Title:	A prospective, Post-Market Clinical Follow-up investigation to verify performance and safety of Otinova® Ear Spray when used in the treatment of external otitis symptoms
Clinical Investigation Code:	CIR_001
Single identification number:	CIV-22-01-038706
Investigational Device(s):	Otinova® Ear Spray
Principal Investigator:	Cristina Ioanes, Carlanderska Sjukhuset, Forskningsenheten, Carlandersparken 1, 412 55 Göteborg
Sponsor:	Circius Pharma AB Södra långebergsgatan 34-36 436 32 Askim Sweden
Date:	09-May-2023

Revision	Version History
A	First release
B	Addition of Site 02
C	Addition of Site 03

This clinical investigation will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. Furthermore, the clinical investigation will be performed in compliance with ISO 14155:2020, Regulation (EU) 2017/745 and applicable regional or national regulations.

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1 SYNOPSIS

NAME OF THE SPONSOR: Circius Pharma AB Södra långebergsgatan 34-36 436 32 Askim Sweden
CLINICAL INVESTIGATION TITLE: A prospective, Post-Market Clinical Follow-up investigation to verify performance and safety of Otinova® Ear Spray when used in the treatment of external otitis symptoms
CLINICAL INVESTIGATION CODE: CIR_001
INVESTIGATIONAL DEVICE(S): Otinova® Ear Spray
OVERALL CLINICAL INVESTIGATION DESIGN: This is a prospective, single-arm, clinical investigation designed to verify performance and safety of Otinova® Ear Spray when used by subjects with external otitis (otitis externa, OE) symptoms in need of treatment. Forty (40) subjects suffering from external otitis symptoms will be recruited from 3 sites in Sweden and receive treatment with Otinova® Ear Spray per instruction for use (twice daily during the test period of 7 days).
INCLUSION AND EXCLUSION CRITERIA: **Inclusion Criteria** The subjects must meet all of the following criteria to be eligible to participate in the clinical investigation: 1. Male or female ≥ 5 years old 2. Clinical diagnosis of otitis externa based on otoscopic exam: a. Defined as a clinical score of at least 1, on a scale from 0 to 2 (none, mild/moderate, severe), for at least one of the OE signs (swelling, erythema and otorrhea) 3. Ability to correctly administer Otinova as spray (not requiring tamponade), as judged by the Investigator 4. Subject agrees to refrain from water immersion of the ears during the investigation 5. Subject agrees to refrain from using other ear treatment products during the investigation 6. Provision of informed consent 7. For pediatric patients, provision of informed consent by subject and legal representative(s) 8. Subject, and if applicable legal representative(s), are willing to comply with the protocol and attend all investigation visits. **Exclusion Criteria** Subjects meeting any of the following criteria will not be permitted to participate in the clinical investigation: 1. Duration of OE signs/symptoms longer than 6 weeks 2. Suspected perforated eardrum or eardrum fitted with drainage tube 3. Post-mastoid surgery

4. Prior otologic surgery within 6 months of enrollment (must be successfully healed)
5. Conditions which may make it difficult to evaluate the therapeutic response (e.g malignant OE, abscess, granulation, polyps, congenital disorders)
6. History of malignant tumors in the external ear canal, or currently receiving chemotherapy or radiation therapy
7. Known allergy or sensitivity to any component of the device
8. Use of topical or systemic antibiotics, corticosteroids or other treatment that could affect the study result within 7 days prior to enrolment
9. Pregnancy or lactation at time of enrolment
10. Subjects with any other condition that, as judged by the investigator, may make investigation procedures inappropriate
11. Participation in another clinical investigation within 30 days of screening

OBJECTIVES:

Primary Objective

- To assess **reduction of swelling, erythema and otorrhea** by Otinova® Ear Spray when used in the treatment of external otitis.

Secondary Objectives

1. To assess the **reduction of itching, otalgia and tenderness** by Otinova® Ear Spray when used in the treatment of external otitis
2. To investigate **reduction of pathologic microbes (bacteria, fungi, yeast)** in the ear canal by Otinova® Ear Spray when used in the treatment of external otitis
3. To assess the **removal of moisture in the ear canal** related to external otitis
4. To assess the **volume of the ear canal**
5. To assess the **user handling** of Otinova® Ear Spray (ease of use of spray, facilitation of correct application)
6. To assess **sleep disruption**
7. To assess **use of pain relief medication**
8. To assess **use of antibiotics**

Safety Objective(s)

- To assess the **safety** of Otinova® Ear Spray.

PERFORMANCE AND SAFETY ENDPOINTS:

Primary Endpoint

Clinical cure – proportion of subjects who have all signs of **swelling, erythema and otorrhea** scored as 0 on a scale from 0-2 (0=none, 1=mild/moderate, 2=severe) after 7 days of treatment, based on otoscopic exam.

Secondary Endpoint(s)

1. **Clinical improvement** – Change in clinical symptoms **itching, otalgia and tenderness**, based on subject reported outcomes, using a score from 0 to 4, where 0 = no symptoms, 1= Mild, 2 = Moderate, 3= Severe and 4 = Very Severe):
    a) Change in each of the clinical symptoms itching, otalgia and tenderness from Day 1 to Day 7
    b) Change in clinical sum score (0-12) of clinical symptoms itching, otalgia and tenderness from Day 1 to Day 7.
    c) Change in each of clinical symptoms (0-4) and clinical sum score (0-12) from Day 1 to Day 3 and Day 5.
2. **Microbiological cure** - Reduction of pathologic microbes in ear canal. Bacteria and fungi/yeast will be analyzed by swabbing the ear canal and analyzing the swab for microbes at baseline and after 7 days of treatment. Microbial cure attained if all pre-therapy pathologic microbes are absent after 7 days of treatment.
3. **Reduced moisture** in ear canal related to otitis externa compared to baseline, based on otoscopic exam. Proportion of subjects who have signs of otorrhea at baseline on a scale from 0-2 (0=none, 1=mild/moderate, 2=severe) and show an improvement of 1 or more points.
4. **Volume of ear canal** compared to baseline – reduced swelling (i.e. increased volume) based on otoscopic exam. Proportion of subjects who have signs of swelling at baseline on a scale from 0-2 (0=none, 1=mild/moderate, 2=severe) and show an improvement of 1 or more points.
5. **User handling -** Ease of use of spray and facilitation of correct application - usability questionnaire
6. **Sleep disruption** – Proportion of subjects with less sleep disruption Day 7 compared to Day 1 - subject diary
7. **Pain relief medication use** - subject diary and medication log
8. **Antibiotic use -** medication log

Safety Endpoint(s)

Incidence of adverse events (AE), adverse device effects (ADE), serious adverse events (SAE), serious adverse device effects (SADE), and device deficiencies (DD) throughout the clinical investigation.

STATISTICAL METHODS:

Performance Analysis

Primary endpoint, clinical cure of swelling, erythema and otorrhea, will be analyzed as proportions of subjects cured with exact 95% confidence interval. Secondary endpoints of cure and improvement will be analyzed in the same way. Categorical variables will be described with numbers, percentages.

Safety Analysis

All safety variables will be tabulated for the Safety Population: AE, ADE, SAE, SADE and DD.

SPONSOR CIP APPROVAL PAGE

The undersigned, hereby confirms that they have read and understood the content of this Clinical Investigation Plan (CIP) and further approves its content.

_____ _____

Mattias Andrup
Medical Affairs Director, Circius Pharma AB

Date (dd-Mmm-yyyy)

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3 ABBREVIATIONS AND ACRONYMS

ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated Serious Adverse Device Effect
CIP	Clinical Investigation Plan
CIR	Clinical Investigation Report
CRF	Case Report Form
CRO	Contract Research Organization
DD	Device Deficiency
DMC	Data Monitoring Committee
DMP	Data Management Plan
DMR	Data Management Report
DVP	Data Validation Plan
EEA	European Economic Area
EU	European Union
FDA	Food and Drug Administration
FIM	First in Man
GDPR	General Data Protection Regulation
IB	Investigator Brochure
ICF	Informed Consent Form
IEC	Independent Ethics Committee
ISF	Investigator Site File
ISO	International Organization for Standardization
MDD	Medical Device Directive – Council Directive 93/42/EEC
MDR	Medical Device Regulation – Regulation (EU) 2017/745
OE	Otitis Externa (external otitis)
PI	Principal Investigator
PMCF	Post-Market Clinical Follow-up
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDV	Source Data Verification
SMF	Study Master File
SOP	Standard Operating Procedure
USADE	Unanticipated Serious Adverse Device Effect
WMA	World Medical Association

4 INTRODUCTION

4.1 Background

Otitis externa (OE), also known as external otitis, is an inflammation/eczema of the ear canal[1, 2]. Many cases of OE involve infection, with *Staphylococcus aureus* and *Pseudomonas aeruginosa* most commonly detected[1, 3, 4], however a large variety of bacteria, fungi and yeast have been identified[4].
OE is also commonly known as 'Swimmer's ear', since one of the most common causes of OE is the prolonged moisture or humidity in the ear canal, typically associated with swimming or humid climates[2]. Other risk factors include trauma to the ear canal, dermatological conditions such as eczema or psoriasis, hearing aid users[2, 5], people with narrow ear canals[1, 2, 5] and under or over production of ear wax[1]. In cases of OE with infection that are not adequately managed, the infection can spread to other parts of the ear causing further complications[4, 6].
Diagnosis is a combination of both signs of ear canal inflammation including swelling, erythema and otorrhea and symptoms including itching, otalgia and tenderness[1, 3, 4].
It is estimated that approximately 10% of the population will be affected at some stage of their lives, including both adults and children[2, 4].

Treatment alternatives for OE includes ear cleaning, earwicks, topical antibiotics, topical steroids and antiseptics (e.g. Burow's solution)[1].

Otinova® Ear Spray is a solution consisting of Aluminium Acetate, Aluminium acetotartrate, Acetic acid and water, with a pH of 3-4, also called Burow's solution. Otinova® Ear Spray is prepared according to the monograph for Burow's solution in the British Pharmacopoeia[7]. Burow's solution is an established treatment for OE[8].

Aluminium Acetate is a combined antiseptic-astringent that has been shown in studies to be as effective as topical antibacterial-corticosteroids at improving cure rates in OE[1, 2]. In *in vitro* studies a 100 % elimination of the bacteria was achieved after up to 40 minutes exposure[9, 10].

When evaluating the effect of Aluminium Acetate on patients suffering from ear infections, it was concluded that Aluminium Acetate is an effective bactericide and high cure rates were reported[10]. In a comparative setting, Aluminium Acetate showed similar cure rates as antibiotics, with low numbers of adverse events reported[11, 12]. Children from 5 years of age who were diagnosed with OE[11] or otitis media[13] were successfully and safely treated with Aluminium Acetate ear drops.

The commercially available Otinova® Ear Spray, containing Burow's solution[14] will be used in this clinical investigation. Burow's solution (including Aluminium Acetate) has been in continuous use since the late 19:th century for treating OE[9]. With the introduction of antibiotics there was a marked decline in its use, but with the emergence of an increasing number of bacteria resistant to first line antibiotics, Burow's solution has got new attention to treat OE[12].

The Clinical Evaluation Report (CER) covering the Otinova® Ear Spray, including data from published clinical investigations using Burow's solution/ Aluminium Acetate, concludes that this device is safe and performs well when used in accordance with its intended use.

The aim of this post-market clinical investigation is to verify performance and safety of Otinova® Ear Spray when used according to its intended use. The target population for this clinical investigation is individuals suffering from external otitis symptoms.

The clinical investigation will be conducted in compliance with the Declaration of Helsinki, ISO 14155:2020, MDR and all approvals (i.e., Independent Ethical Committee (IEC) and if applicable biobank approval) will be retrieved before investigation initiation. The clinical data retrieved from this clinical investigation will be evaluated and incorporated into the products CER.

The costs associated with the investigation are financed by the Sponsor on a per subject basis, as described in the clinical investigation agreement between Sponsor and the investigation site.

5 IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATIONAL DEVICE

Otinova® Ear Spray is a spray used to treat ear canal inflammation/eczema, also known as Swimmer's Ear (external otitis). Otinova® Ear Spray acts locally, as an astringent, relieves itching and has an antibacterial and anti-fungal effect. The device is CE-marked and classified as Class I according to MDD Classification rule 5[15] and has been on the market since 2011.

5.1 Manufacturer

The legal manufacturer for the investigational medical device is:

Circius Pharma AB
Södra långebergsgatan 34-36
436 32 Askim, Sweden

5.1 Identification of Investigational Medical Device

Otinova® Ear Spray is a spray solution enclosed in a plastic bottle with an attached spray nozzle.

[redacted]

[redacted]

[redacted]

5.2 Device Traceability

The Sponsor and the Principal Investigator (PI) will keep records documenting the location of all investigational devices from shipment to the investigation site until the end of the clinical investigation. This will be documented in a shipment log stored by the Sponsor and in a device accountability log at the investigation site. The device accountability log at site will include information on:

- date, lot number and expiry date for each delivered device,
- date and subject identification for each dispensed device,
- date for each device returned to Sponsor from site (if applicable)

The investigational devices will be handled and stored safely, properly and in agreement with the provided storage conditions in the Instructions for Use (IFU)[8].

The monitor will verify the accountability process at site and document this in the site monitoring visit report.

5.3 Intended Purpose

Otinova® Ear Spray is intended be used to treat external otitis, e.g. in connection with periods of frequent contact with water and/or damp environments, such as swimming/aquatic sports holidays.

5.4 Indication and Population

Otinova® Ear Spray is intended to be used by individuals to treat ear canal inflammation/eczema, also known as Swimmer's Ear (external otitis). Otinova® Ear Spray is intended to be used in adults and in children over 5 years.

5.5 Technical and Functional Features

Otinova® Ear Spray is filled in a transparent, 20 mL, PE, sterilized bottle. The bottles are closed with Spray cord and fitted with a 3K pump which functions both as a microbiological safeguard and as a dosing system. A transparent cover is placed over the spray cork. A label is placed onto the bottle. Each bottle is placed in a labelled carton with one IFU.

5.6 Manufacturing and Materials

Manufacturing and packaging of the Otinova® Ear Spray are conducted according to Good Manufacturing Practice (GMP) and ISO 13485.

No medicinal substances, human or animal tissues or derivates thereof, or their biological active substances, are incorporated in Otinova® Ear Spray. Consequently, no such materials will be in contact with any tissues or body fluids.

5.7 Training and Experience

Investigator and site personnel training will be conducted by sponsor and Contract Research Organization (CRO) representatives prior to subject enrollment to ensure that the Otinova® Ear Spray device is used in accordance with the IFU, that complete, accurate and timely data are submitted, that protocol requirements are followed, and that complications, adverse events (AEs) and adverse device effects (ADEs) are correctly reported and investigated, as appropriate. The investigator will ensure that appropriate training relevant to the clinical investigation is given to any

other site personnel involved in the investigation and that new information of relevance to the performance of the investigation is forwarded to all personnel involved.
It is the responsibility of the sponsor to ensure that involved personnel is appropriately trained on the Otinova® Ear Spray device. Since the subjects will treat themselves with the Otinova® Ear Spray device following the IFU, it is the responsibility of the site personnel to provide guidance as required.

5.8 Installation and Use

The device should be used according to the IFU, as shown below:

- To use Otinova® Ear Spray, hold the bottle upright.
- Before the spray is used for the first time, pump a few times until an even spray is obtained.
- Hold the tip of the nozzle against the outer ear canal.
- Spray 1–2 times in the ear canal, morning and evening.
- Tilt the head after spraying so that the fluid runs as far as possible down into the ear canal.
- Wipe away any excess fluid.
- Otinova® Ear Spray should be used two times per day (morning and evening) for up to 7 days.

Warnings and precautions

- Otinova® Ear Spray can cause temporary mild irritation/stinging sensation in the ear canal. If the irritation/stinging persists or becomes worse, contact a doctor.
- Avoid contact with water and do not poke inside the ear.
- Otinova® Ear Spray should not be used by children younger than 5 years of age, unless recommended by a doctor (control of the eardrum).
- Salt precipitation in, and severe hydration of, the ear canal may occur with overdosing and/or long-term use. Do not use Otinova® Ear Spray for a continuous period of more than 7 days.
- Otinova® Ear Spray should not be used if the eardrum has been fitted with a drainage tube or if the eardrum is suspected to be perforated.

6 JUSTIFICATION OF CLINICAL INVESTIGATION DESIGN

As per MEDDEV 2.12/2 rev.2 the decision to conduct a Post-Market Clinical Follow-up (PMCF) investigation has been based on the identification of possible residual risks and/or unclarity on long term clinical performance that may impact the benefit/risk ratio. The rationale behind the PMCF investigation is that the initial CE-marking of the Otinova® Ear Spray was based on equivalence, (which is highlighted as one of the circumstances that may justify a PMCF clinical investigation in the MEDDEV document) and the increased demand for clinical data under Regulation (EU) 2017/745 (MDR). Thus, the PMCF investigation is aiming at confirming the clinical performance and safety of the Otinova® Ear Spray, when used according to its approved labelling, to create further support for the current claims and intended use.

The PMCF investigation including the Otinova® Ear Spray is planned to start during 2022 at three sites in Sweden. In total 40 subjects will be included. The PMCF investigation is planned to confirm that the Otinova® Ear Spray continues to demonstrate safety and performance in a population with external otitis symptoms when Otinova® Ear Spray is used as intended.

This PMCF investigation is designed as a prospective, multi-center, single-arm, clinical investigation to verify clinical performance and safety of the Otinova® Ear Spray as a treatment for external otitis symptoms. The objectives of the investigation are to confirm treatment of symptoms by Otinova® Ear Spray when used by subjects with external otitis symptoms when used as intended.

The follow-up period during the clinical investigation is deemed sufficiently to represent a realistic test of the performance of the investigational device and allows any risks associated with adverse device effects over that period to be identified and assessed.

7 BENEFITS AND RISKS OF THE INVESTIGATIONAL DEVICE, CLINICAL PROCEDURE, AND CLINICAL INVESTIGATION

When discussing risks and benefits of a medical device, there are different aspects that have to be considered, including the potential risks and benefits for the subjects participating in the clinical investigation and for future patients with clinical use of the device.

Risk management, including risk analysis, risk evaluation and risk control, related to the devices has been conducted in accordance with ISO 14971 and the manufacturer's risk management procedure[17].

7.1 Anticipated Clinical Benefits

The anticipated clinical benefit of Otinova® Ear Spray includes the treatment of ear canal inflammation/eczema. [redacted]

7.2 Residual Risks and Anticipated Adverse Device Effects

Residual risks are described in alignment with the approved versions of the products' risk management report.

[redacted]

[redacted]

7.3 Risks Associated with Participating in the Clinical Investigation

Investigation participation is not considered to expose subjects to new device-related risks. The clinical investigation procedures follow routine clinical practice except for the microbial swab sampling from the ear canal, diary and questionnaires. There may potentially be minor additional discomfort for participants as a result of the swab sampling. There may also potentially be minor inconvenience for the subjects in the additional assessment time or clinical visits. This is to ensure data collection of all variables including those reported by the subject.

7.4 Possible interactions with concomitant medical treatments

There are no known interactions with concomitant medical teratments.

7.5 Risk Control

The investigational device shall be used in accordance with the intended use and IFU. The investigation team will receive training on the CIP prior to the first subject's first visit.

Risks related to the processing of subjects' personal data, and in particular data concerning health, will be mitigated by use of pseudonymization, whereby the personal data will no longer be attributable to a specific subject without the use of a key which will be kept separately and securely by the PI.

Risk management for the investigational device has been conducted by first identifying the possible hazards, foreseeable sequences of events and possible harms, and then evaluating and mitigating the risks. The following risk control measures have been used in the priority order listed:

1. Eliminate or reduce risks as far as possible (inherent safety by design).
2. Protective measures in the medical device itself or in the manufacturing process.
3. Information to the user of the residual risk due to any shortcomings of the protection measures adopted.

All risks have been reduced as far as possible, meaning that all safety principles have been applied where possible and where safety could be improved.

7.6 Benefit-to-Risk Rationale

Risk management for the investigational device concluded that the clinical benefit of using the device outweigh the residual risks. The investigational devices have been on the market for many years and shown to be a low-risk device.

It is not anticipated that the investigational procedures not part of routine clinical practice, e.g., ear swab sampling, questionnaires and diary will expose the subjects to additional risks, except for a low possibility of discomfort during the swab sampling.

Risks related to the processing of subjects' personal data will be mitigated by use of pseudonymization.

The additional time for assessment is considered as limited and thus acceptable.

The potential benefits identified for participants of the investigation are more control measures than in normal clinical practice to ensure compliance to standard of care. Due to this, there is a chance of obtaining better treatment outcomes. Second, there is dedicated time at the clinic to ensure realization of this investigation and collection of all included outcome assessments. This may result in more time with clinical experts for the participating subjects than in normal clinical care and that follow-up and care is less subjected to time restrictions and resources limitations.

This clinical investigation will be conducted in line with applicable regulations and ethical principles designed to safeguard investigation subjects. The PI will ensure that appropriate training relevant to the investigation is provided to the staff involved. The reporting of adverse events and monitoring described in Section 18 and 10 respectively, will assure early detection of any increased risk or unanticipated subject safety concerns.

Taken together, the possible benefits for a subject in participating in this clinical investigation are considered to outweigh the possible risks.

8 OBJECTIVES AND HYPOTHESES OF THE CLINICAL INVESTIGATION

8.1 Primary Objective

The primary objective is:

- To assess **reduction of swelling, erythema and otorrhea** by Otinova® Ear Spray when used in the treatment of external otitis.

8.2 Secondary Objectives

The secondary objectives are:

1. To assess the **reduction of itching, otalgia and tenderness** by Otinova® Ear Spray when used in the treatment of external otitis
2. To investigate **reduction of pathologic microbes (bacteria, fungi, yeast)** in the ear canal by Otinova® Ear Spray when used in the treatment of external otitis
3. To assess the **removal of moisture in the ear canal** related to external otitis
4. To assess the **volume of the ear canal**
5. To assess the **user handling** of Otinova® Ear Spray (**ease of use of spray, facilitation of correct application)**
6. To assess **sleep disruption**
7. To assess use of **painrelief medication**
8. To assess use of **antibiotics**

8.3 Hypothesis

The null hypothesis (H_0) is that less than 50% of the subjects will be cured regarding swelling, erythema and otorrhea.

The H_1 is that more than 50% of the subjects will be cured regarding swelling, erythema and otorrhea.

8.4 Claims and Intended Performance of the Investigational Device

The claims to be verified in this investigation are:

1. Due to the low pH, Otinova® Ear Spray may help the removal of moisture in the ear canal related to external otitis or inflammation of the ear canal.
2. Due to the astringent effects of aluminium acetate, Otinova® Ear Spray has an astringent effect on inflamed tissue on the ear canal, thereby increasing the volume of the ear canal.
3. Due to the composition, Otinova® Ear Spray may provide a soothing effect on itch within the ear canal associated with inflammation/external otitis.
4. Otinova® Ear Spray is designed to be administered in the form of spray, helping to make it easy to use.
5. Otinova® Ear Spray has an anatomically designed nozzle to help facilitate correct application.

6. Otinova® Ear Spray has a bactericidal and fungicidal effect in the ear canal.
7. Otinova® Ear Spray can be used in children over the age of 5 years.
8. Where used as first line treatment and an effective outcome is achieved, Otinova® Ear Spray may reduce the need for antibiotics.

8.5 Risks and Anticipated Adverse Device Effects

There are no anticipated Adverse Device Effects for the investigational devices and no unacceptable risks connected to participating in the investigation.

9 DESIGN OF THE CLINICAL INVESTIGATION

9.1 General

This is a prospective, open, multi-centre, single-arm clinical investigation designed to verify performance and safety of Otinova® Ear Spray when used by subjects with external otitis symptoms in need of treatment. The outcome will be evaluated and incorporated in the product specific CER and serve as a base for continuous investigations.

Following EC approval, 40 subjects suffering from external otitis symptoms will be recruited from three sites in Sweden and receive treatment with Otinova® Ear Spray per instruction for use (twice daily during the test period, for 7 days). Three visits are planned for each subject, including a screening/baseline visit at the clinic, a follow-up visit at the clinic and a follow-up telephone visit to assess any safety issue. If considered necessary by the investigator, study nurse or subject, additional contacts (e.g., visits/phone calls/video calls) can be arranged.

The overall duration of the investigation is estimated to five months, including a four-month recruitment period. Expected duration of each subject's participation is 14 days. The investigation will be considered complete when the last subject has completed the last visit.

9.1.1 Primary performance endpoint

- **Clinical cure** – proportion of subjects who have all signs of **swelling, erythema and otorrhea** scored as 0 on a scale from 0-2 (0=none, 1=mild/moderate, 2=severe) after 7 days of treatment, based on otoscopic exam.

9.1.2 Secondary performance endpoints

1. **Clinical improvement** – Change in clinical symptoms **itching, otalgia and tenderness**, based on subject reported outcomes, using a score from 0 to 4, where 0 = no symptoms, 1= Mild, 2 = Moderate, 3= Severe and 4 = Very Severe):
    a. Change in each of the clinical symptoms itching, otalgia and tenderness from Day 1 to Day 7
    b. Change in clinical sum score (0-12) of clinical symptoms itching, otalgia and tenderness from Day 1 to Day 7.
    c. Change in each of clinical symptoms (0-4) and clinical sum score (0-12) from Day 1 to Day 3 and Day 5.

2. **Microbiological cure** - Reduction of pathologic microbes in ear canal. Bacteria and fungi/yeast will be analyzed by swabbing the ear canal and analyzing the swab for microbes at baseline and after 7 days of treatment. Microbial cure attained if all pre-therapy pathologic microbes are absent after 7 days of treatment.

3. **Reduced moisture** in ear canal related to otitis externa compared to baseline, based on otoscopic exam. Proportion of subjects who have signs of otorrhea at baseline on a scale from 0-2 (0=none, 1=mild/moderate, 2=severe) and show an improvement of 1 or more points.

4. **Volume of ear canal** compared to baseline – reduced swelling (i.e. increased volume) based on otoscopic exam. Proportion of subjects who have signs of swelling at baseline on a scale from 0-2 (0=none, 1=mild/moderate, 2=severe) and show an improvement of 1 or more points.

5. **User handling -** Ease of use of spray and facilitation of correct application – usability questionnaire

6. **Sleep disruption** - Proportion of subjects (and parents) with less sleep disruption Day 7 compared to Day 1, reported in subject diary.

7. **Painrelief medication use** - subject diary and medication log

8. **Antibiotic use -** medication log

9.1.3 Secondary safety endpoints

Incidence of adverse events (AE), adverse device effects (ADE), serious adverse events (SAE), and serious adverse device effects (SADE), and device deficiencies (DD) throughout the clinical investigation.

9.2 Investigational Device(s) and Comparator(s)

This PMCF will not use a comparator as baseline values are used as controls.

Subjects will use the investigational devices for a total of 7 days, where the investigational device Otinova® Ear Spray, is used twice daily during the complete test period. At baseline visit, Visit 1, the subjects will receive one bottle of Otinova® Ear Spray which is sufficient for treatment during the entire investigational period.

9.3 Subjects

9.3.1 Inclusion Criteria

The subjects must meet all of the following criteria to be eligible to participate in the clinical investigation:

1. Male or female ≥ 5 years old
2. Clinical diagnosis of otitis externa based on otoscopic exam:
    a. Defined as a clinical score of at least 1, on a scale from 0 to 2 (none, mild/moderate, severe), for at least one of the OE signs (swelling, erythema and otorrhea)
3. Ability to correctly administer Otinova as spray (not requiring tamponade), as judged by the Investigator
4. Subject agrees to refrain from water immersion of the ears during the investigation
5. Subject agrees to refrain from using other ear treatment products during the investigation
6. Provision of informed consent

7. For pediatric patients, provision of informed consent by subject and legal representative(s)
8. Subject, and if applicable legal representative(s), are willing to comply with the protocol and attend all investigation visits.

9.3.2 Exclusion Criteria

Subjects meeting any of the following criteria will not be permitted to participate in the clinical investigation:

1. Duration of OE signs/symptoms longer than 6 weeks
2. Suspected perforated eardrum or eardrum fitted with drainage tube
3. Post-mastoid surgery
4. Prior otologic surgery within 6 months of enrollment (must be successfully healed)
5. Conditions which may make it difficult to evaluate the therapeutic response (e.g malignant OE, abscess, granulation, polyps, congenital disorders)
6. History of malignant tumors in the external ear canal, or currently receiving chemotherapy or radiation therapy
7. Known allergy or sensitivity to any component of the device
8. Use of topical or systemic antibiotics, corticosteroids or other treatment that could affect the study result within 7 days prior to enrolment
9. Pregnancy or lactation at time of enrolment
10. Subjects with any other condition that, as judged by the investigator, may make investigation procedures inappropriate
11. Participation in another clinical investigation within 30 days of screening

During the investigation, subjects are asked to avoid water inside the ears, by using earplugs or cottonswabs during shower and bath. Additionally, subjects are asked to refrain from swimmingpools and swimming outdoors. The use of in-ear headphones or removable hearing aids should if possible be avoided during treatment. Subjects are also asked to avoid poking inside the affected ear.

9.3.3 Relationship of Investigation Population to Target Population

The investigational product, Otinova® Ear Spray, aims to be used by children and adults in a home environment. Otinova® Ear Spray can be used by healthcare professionals. No training before use is required. In this clinical investigation Otinova® Ear Spray can be used in all subjects with the following exceptions, as stated in the IFU:

- Otinova® Ear Spray should not be used by children younger than 5 years of age
- Otinova® Ear Spray should not be used if the eardrum has been fitted with a drainage tube or if the eardrum is suspected to be perforated.

The investigation population, characterized by children from 5 years of age (see Section 19, Vulnerable population) and adults suffering from extern otitis symptoms, represents the target population.

9.3.4 Number of Subjects

A total of 40 subjects will be included in the clinical investigation, who are fulfilling all the inclusion criteria and none of the exclusion criteria for the clinical investigation. For details linked to sample size calculations, see section 11.2.

9.3.5 Methods of Assigning Subjects to Different Treatment Arms

Not applicable, all subjects will receive the same treatment.

9.3.6 Subject Withdrawal, Discontinuation, or Lost to Follow-up

Subjects are free to discontinue participation in the clinical investigation at any time and are not required to give a reason for their decision. However, subjects who discontinue the investigation should always be asked about the reason(s) for their discontinuation and about the presence of any adverse event (AE) /adverse device effect (ADE) and, if possible, be assessed by an investigator. Discontinuation from the clinical investigation will not affect the future treatment /care of the subject.

If the subject want to withdraw his / her consent no further data will thereafter be recorded. Data collected up to the date of withdraw of informed consent will be used in the data analysis and for the Clinical investigation Report (CIR).

Subjects may be withdrawn from the clinical investigation and assessments at any time, if deemed necessary by the PI.

Specific reasons for withdrawal of subjects from this clinical investigation are:

- The decision of a subject to withdraw from the investigation (including if the subject withdraws informed consent)
- The PI deems the subject unfit for the investigation or suspects poor CIP compliance;
- It becomes apparent that the subject no longer meets the eligibility criteria
- The PI decides to end the treatment with Otinova® Ear Spray (for details see section 9.3.7)
- Subject lost to follow-up.

In case of withdrawal, all AEs/ADEs should be followed up. Questionnaires and diaries should be collected, if possible.

Incorrectly enrolled subjects will be withdrawn from further investigation and assessments.

To meet the target of 40 subjects completing the investigation, subjects may be replaced if they no longer meet the eligibility criteria whilst participating in the investigation and the recruitment is still ongoing. In order to ensure inclusion of at least 7 children, the inclusion of subjects 18 years and older will pause when reaching 33 included adult subjects (see sample size calculations, section 11.2). In case of prolonged enrolment period due to possible slow inclusion of children,

the Sponsor has the right to decide whether to instead continue inclusion of adults to reach a total of 40 subjects.

9.3.7 Subject Follow-up and Care

Each subject will be treated with Otinova® Ear Spray for 7 days. There will be one follow-up visit after 7 days of treatment and an additional follow-up, 14 days after the start of treatment to assess any safety issues.

If symptoms increase or new symptoms occur (e.g. increased redness, oedema and/or fever), the PI should be contacted immediately by phone. The PI decides how to proceed with further treatment and an additional visit (recorded as "unscheduled visit") at the clinic is scheduled.

If symptoms are unchanged after 3 days, the subject should contact the PI by phone. The PI decides how to proceed with treatment (continuation of use of Otinova® Ear Spray or alternative treatment). An additional visit at the clinic (recorded as "unscheduled visit") can be made if deemed necessary by the PI.

Any additional treatment shall be recorded in the subject's medical record and in the Medication log. Increased or new symptoms shall be recorded as Adverse Events (see section 18.3).

If the PI decides to end the treatment with Otinova® Ear Spray, the subject will be withdrawn from the investigation.

Please see Section 9.3.6 for procedures that will be taken for subjects that withdraw, discontinue, or are lost to follow-up.

At Visit 2, remaining devices will be collected, and subjects will not be allowed to retain remaining devices. The same applies should the investigation be temporarily halted, or early terminated. After exit, no additional medical care is needed or required, and no additional follow-up is needed. It is the responsibility of the PI to follow-up AE:s still ongoing at the end of the investigation.

9.4 Clinical Investigation Duration

Point of enrolment:	May 2022
Enrolment period:	May 2022-August 2023
Expected duration of each subject's participation:	14 days
Total expected duration of the clinical investigation:	5 months

9.5 Clinical Investigation Procedures

The assessments and procedures that will be performed during the clinical investigation are shown in the table "Schedule of Clinical Investigation Procedures/ Assessments".

9.5.1 Schedule of Clinical Investigation Procedures /Assessments

Assessment	Visit 1 Screening/ Baseline	Visit 2 Follow-up	Visit 3 Follow-up
	Day 1	Day 8 (+2 days)	Day 14 (+/- 1 day)
Subject information sheet and informed consent	X		
Subject demographics[1]	X		
Inclusion/Exclusion criteria	X		
Relevant medical and surgical history	X		
History of OE[2]	X		
Pregnancy test (fertile women)	X		
Otoscopic exam incl. score	X	X	
Microbial swab testing	X	X	
Concomitant medication	X	X	X
Adverse event questions	X	X	X
Device instructions, start of treatment	X		
Diary[3] **instructions**	X		
Diary review and collection		X	
Device collection		X	
Usability questionnaire[4]		X	
End of investigation			X

Notes:
[1] Age, gender, height, weight, BMI
[2] Including previous episodes of OE, duration of diagnosis/age of onset, hearing impairment
[3] Diary for collecting data of device usage, symptoms, ear pain medication use, impact of ear pain on sleep
[4] Usability questionnaire including assessment of ease of use of spray and application

9.5.2 Recruitment of subjects

Subjects will be recruited via advertising. Candidates interested in participating in the study will be contacted by the clinic via a telephone call and a pre-screening will be performed to make a primary assessment of whether the candidate could be suitable for the investigation or not. Candidates who at this time are interested in participation will be scheduled for a first visit at the clinic, Visit 1.

9.5.3 Visit 1 (Day 1) Screening / Baseline Visit

Before any investigation-related procedures are initiated, the informed consent must be signed and dated by the subject (or their legally acceptable representative and/or witness, as applicable) and by the Investigator who gave the subject the verbal and written information. The original

document will be retained in the Investigator Site File (ISF) and a copy provided to the subject. The investigator must obtain written informed consent from the subject before any clinical investigation-related procedures are performed, for further details on the informed consent process please see section 17.
In case of bilateral disease, the most severely affected ear, according to PI:s judgment, will be selected (subject are allowed to use Otinova® Ear Spray to treat both ears at home, but only the selected ear will be analyzed as part of the investigation).

At Visit 1, Day 1 (Clinic visit), the following assessments will be performed:

- Demographics:
  - Age
  - Gender
  - Height
  - Weight
  - BMI
- Pregnancy test, if female and fertile
- Relevant Medical & Surgical history
- History of OE
  - Previous episodes of OE
  - Duration of diagnosis/age of onset
  - Hearing impairment
- Relevant concomitant medication
- Inclusion /Exclusion criteria
- Otoscopic exam incl. score (score of selected ear in case of bilateral disease). Including cleaning of the ear, needed for diagnosis, as deemed by the Investigator.
- Microbial swab testing (of selected ear in case of bilateral disease)
- Diary instructions
- Training of how to use the device – The subject will initiate the treatment under supervision at the clinic
- Adverse events questions

9.5.4 Visit 2 (Day 8 +2 days) – Clinic visit

At visit 2 the following assessments will be performed:

- Otoscopic exam incl. score (score of selected ear in case of bilateral disease)
- Microbial swab testing (of selected ear in case of bilateral disease)
- Concomitant medication
- Adverse events questions
- Diary review and collection
- Device collection
- Usability questionnaire

9.5.5 Visit 3 (Day 14 +/- 1 day) – Telephone visit

- Adverse events questions
- Concomitant medication
- End of investigation

9.5.6 Unscheduled visits /contacts

If deemed necessary for any reason, e.g., if OE symptoms are increased or unchanged (see Section 9.3.7) or AEs/ADEs, additional unscheduled visits may be conducted within the course of the clinical investigation. Unscheduled visits may be conducted at site or as a telephone or video call. All unscheduled visits shall be documented in the eCRF and in the subjects' medical notes, as applicable.

9.5.7 Screening/Baseline Measurements

9.5.7.1 Demographic data

At the screening/baseline visit, the following demographic data is to be collected for the subject: age, gender, height, weight and BMI. If applicable a pregnancy test will be performed in fertile women.

9.5.7.2 Medical and surgical history

At visit 1, relevant medical and surgical history e.g. previous otologic surgery, diabetes, hypertonia will be documented for each subject. The history regarding relevant diagnoses will be recorded. The medical history will be used to assess the subject for any disqualifying medical conditions as specified in the exclusion criteria.

9.5.7.3 History of Otitis Externa

At visit 1, history of OE will be collected, including:

- previous episodes of OE
- duration of diagnosis/age at onset
- hearing impairment

9.5.7.4 Otoscopic exam of the ear

An otoscopic exam of the ear will be conducted at clinic visits by the investigator, using an otoscope and/or microscope. The otoscopic exam will provide information related to OE and includes OE scores for swelling, erythema and otorrhea.

9.5.7.5 Microbial testing

A microbial testing of the earcanal, by using a swab, will be performed at clinic visits by site personnel. The microbial swab sample will be analyzed for pathologic microbes (bacteria and fungi/yeast).

9.5.7.6 Concomitant medication

At visit 1, relevant prior and all concomitant medication will be collected for each subject. The prior/concomitant medication will be used to assess the subject for any disqualifying medication

as specified in the exclusion criteria. The subject will be instructed to report ear-pain medication in the diary. Concomitant medication, including the diary, will be reviewed at the subsequent visits.

9.5.8 Performance Variables and Measurements

9.5.8.1 OE signs

Changes of OE signs between baseline (Visit 1) and after 7 days of treatment (Visit 2) using a 3-point scale (0 = none, 1 = mild/moderate, 2 = severe), by otoscopic exam. Analyzed as proportion of subjects with all signs of swelling, erythema and otorrhea scored as 0. Also, a sum score will be created for swelling, erythema and otorrhea. This sum score will be handled as a continuous variable.

Score	Definition	Description
Swelling		
0	None	Absent
1	Mild/Moderate	Partly occluded ear canal
2	Severe	Complete or almost complete occluded ear canal
Erythema (redness)		
0	None	Absent
1	Mild/Moderate	A light or clearly visible redness of skin in the ear canal
2	Severe	Intense redness of skin in ear canal
Otorrhea (moisture)		
0	None	Absent
1	Mild/Moderate	Visible secretions in parts of the ear canal
2	Severe	Secretions that completely or partly obscure the tympanic membrane

9.5.8.2 OE symptoms

Changes of OE symptoms **itching, otalgia and tenderness** using a score from 0 to 4, where 0 = no symptoms, 1= Mild, 2 = Moderate, 3= Severe and 4 = Very Severe, as reported by the subject in a diary. Analyzed as:

a. Change in each of the clinical symptoms itching, otalgia and tenderness from Day 1 to Day 7. These variables will be regarded as ordered categorical and will be described by visit and by change (improved, no change and not improved).
b. Change in clinical sum score of clinical symptoms itching, otalgia and tenderness from Day 1 to Day 7, based on the sum of the three scores (0-12).
c. Change in clinical symptoms from Day 1 to Day 3 and Day 5.

9.5.8.3 Pathologic microbes by microbial sampling

Prescence of pathologic microbes in the ear canal will be assessed by a microbial swab sample. Two (2) samplings will be performed, the first at Visit 1 and the second sampling at Visit 2. The

microbial sample will be analyzed for pathologic microbes; bacteria and fungi/yeast. The testing will be performed according to the clinic's routines for swab sampling and the samples will be placed in a refrigerator as soon as possible after sampling. The samples will be pseudonymized by labelling with Subject ID and Visit number. The samples will be shipped daily to the laboratory Unilabs (Skövde, Sweden) or Synlab (Stockholm, Sweden) for analysis. These are accredited laboratories, fulfilling the requirements in SS-EN ISO 15189 and ISO/IEC 17025:2018. The result of the analysis is the bacterial and fungal species, which could be, but are not limited to, *Staphylococcus aureus* and *Pseudomonas aeruginosa*. The samples will be destroyed immediately (within 1-2 days) after analysis.

9.5.8.4 Moisture in the ear canal

Reduction of moisture in the ear canal, otorrhea, between baseline (Visit 1) and after 7 days of treatment (Visit 2), by otoscopic exam, using a 3-point scale (0 = none, 1 = mild/moderate, 2 = severe), by otoscopic exam. Analyzed as proportion of subjects with signs of otorrhea at baseline on a scale from 0-2 (0=none, 1=mild/moderate, 2=severe) and show an improvement of 1 or more points.

9.5.8.5 Volume of ear canal

Change of volume of the ear canal between baseline (Visit 1) and after 7 days of treatment (Visit 2), by otoscopic exam, using a 3-point scale (0 = none, 1 = mild/moderate, 2 = severe). Reduced swelling of the ear canal results in increased volume of the ear canal. Analyzed as proportion of subjects with signs of swelling at baseline on a scale from 0-2 (0=none, 1=mild/moderate, 2=severe) and show an improvement of 1 or more points.

9.5.8.6 User handling

Subject experience of user handling of Otinova will be captured at visit 2, through a paper questionnaire to be filled out by the subject. The questionnaire will contain questions regarding ease of use of spray and ease of application. Each question will be answered by the subject by choosing the most correct answer on a scale or replying on a yes or no question.

9.5.8.7 Subject diary

A subject diary will be used for collecting data of:

- Device usage compliance (morning and evening, yes/no)
- OE symptoms experienced (itching, ear pain, tenderness, scale 0-4, see Section 9.5.8.2)
- Impact of ear pain on sleep (yes/no), if children: Impact on parents' sleep (yes/ no), see Section 9.5.8.8
- Ear pain medication use (yes/no), see Section 9.5.8.9

9.5.8.8 Sleep disruption

Sleep disruption of subject and parent as reported in subject diary. Analyzed as proportion of subjects with less sleep disruption Day 7 compared to Day 1 and proportion of parents with less sleep disruption Day 7 compared to Day 1.

9.5.8.9 Use of ear pain medication

Use of pain relief medication for ear pain, as reported in subject diary, replying on a yes or no question.

9.5.8.10 Use of antibiotics

Use of antibiotics for OE symptoms, as listed in Medication log.

9.5.9 Safety Variables and Measurements

All incidences of AEs and DDs will be documented and reported during the clinical investigation. AEs will be categorized as AE, ADE, SAE, or SADE. For details related to AE definitions or reporting, please see Section 18.
All events will be followed up until resolved or judged as clinically stable according to the investigator, if possible.

From baseline and at all follow-up visits the study personnel will ask the subject if they have experienced any adverse events since last visit. The diary will be checked for any new symptoms that occurred, together with any new or change in medication.

9.5.10 Activities Performed by Sponsor

The Sponsor is responsible for device training of involved personnel. Device training will be documented in applicable training logs.
Sponsor is also responsible for reporting of DDs discovered by the sponsor.
Reporting of SAEs according to Section 18.5.

9.5.11 Potential Confounding Factors

The use of other OE treatments is a potential confounding factor, which is addressed by subject eligibility criteria and in the information provided to subjects. Subject illness, particularly infections, during investigation participation is a potential confounding factor, which is addressed by adverse event reporting.

9.5.12 Samples obtained from subject

The samples obtained will be destroyed immediately after analysis (latest within 1-2 days after analysis).

10 MONITORING PLAN

A detailed description of monitoring activities will be provided in a separate, investigation-specific risk-based monitoring plan.

10.1 Subject Records and Source Data

Subject data recorded directly in electronic case report form (eCRF) (and not into the medical record) will be considered source data. It is the responsibility of the PI to record essential information in the medical records, in accordance with national regulations and requirements. The origin of source data in this clinical investigation will be further specified in a separate document ("Source Data Location Agreement").

It is the responsibility of the PI to record essential information in the medical records, in accordance with national regulations and requirements.

In general the following information should be recorded in the medical records:

- Investigation code, and or investigational title
- Subject screening number and/or subject ID
- That informed consent for participating in the clinical investigation was obtained, and the date of collection
- Diagnosis
- All visits during the investigation period including visit date
- All AEs
- Treatments and medications
- Subject health service identification number, if applicable

The PI is responsible for ensuring the accuracy, completeness, legibility and timeliness of the data recorded in the eCRFs. Signed sections of eCRFs will be monitored on a regular basis.

10.2 Access to Source Data and Documentation

The PI should guarantee access to source documents for the monitor and auditors as well as for inspection by appropriate Regulatory Agencies / Competent Authorities, and Independent Ethics Committees (IECs), if required.

11 STATISTICAL CONSIDERATIONS

11.1 Statistical Design, Method and Analytical Procedures

This is a single arm investigation with no comparison group. No randomization will be performed. Both intention to treat (ITT) analyses, as well as per protocol analyses (PP) will be performed. Both the ITT and the PP population will be defined at the Clean File meeting before the database lock. All included subjects who started treatment will be included in the safety analysis set (SAF).
Continuous variables are described with mean, SD, median and range and categorical variables with numbers and percentages.
Change in dichotomous and ordered categorical variables will be performed with Sign test and change in continuous variables will be performed with Fisher's non-parametric permutation test for paired observations. Proportions of cured and improved will be given with exact 95% confidence interval.
No adjustment for confounders can be performed due to the single arm design.
The primary analysis, clinical cure of swelling, erythema and otorrhea, will be analyzed as proportions of subjects cured with exact 95% confidence interval. A Sum score will be created for swelling, erythema and otorrhea. This sum score will be handled as a continuous variable.
Secondary endpoints of cure and improvement will be analyzed in the same way.

All significance tests will be two-sided and conducted at the 5% significance level.

11.2 Sample size

In order to show that the lower limit of the exact 95% confidence interval for the proportion cured regarding swelling, erythema and otorrhea will be higher than 50% with a probability of 80%, given a 0.75 proportion of cured at significance level 0.05, 33 evaluable subjects are needed. A drop-out rate of 10% is assumed and hence the sample size needs to be a minimum of 37 subjects. In order to account fo drop-outs as well as the inclusion of both children and adults, a sample size of 40 subjects was therefore chosen.

11.3 Drop-out Rates

A drop-out rate of 10% is expected.

11.4 Level of Significance and Power

Power for primary analysis is 80% and significance level 0.05. Where possible 95% confidence intervals will be given.

11.5 Pass / Fail Criteria

Pass criteria is to show that percentages cured regarding swelling, erythema and otorrhea is significantly higher than 50%.

11.6 Interim Analysis

No interims analysis will be performed.

11.7 Reporting of Deviations from the Original Statistical Analysis Plan (SAP)

Any changes from the original Statistical Analysis Plan (SAP) will be amended in a revised SAP.

11.8 Subgroups for Analysis

For the following subgroups, proportion cured regarding swelling, erythema and otorrhea with exact 95% CI and proportion improved regarding itching, otalgia and tenderness with exact 95% CI will be calculated:

- Age 5-17
- Age 18 and over

11.9 Procedures that Take into Account all the Data

All ITT analyses will take into account of all data.

11.10 Missing, Unused or Spurious Data

Outliers will be included in summary tables and listings, and will not be handled separately. Available data from prematurely withdrawn subjects will be included in the analysis as far as possible. Missing data will be analyzed and imputed with appropriate method.

11.11 Exclusion of Particular Information from the Testing of the Hypothesis

No exclusion of particular information from the testing of the hypothesis is planned.

12 DATA MANAGEMENT

Data management and handling will be conducted according to the investigation specific Data Management Plan (DMP) in accordance with applicable guidelines and CRO:s Standard Operating Procedures (SOPs). Any deviations, i.e. discrepancies and additions from the process defined in the DMP will be described in an investigation specific Data Management Report (DMR).

Data will be collected in eCRFs specifically designed for this clinical investigation. The Principal Investigator or any other authorized person will record subject data in the eCRF in a precise and accurate manner. Abbreviations should not be used unless otherwise instructed in the Data Entry Instruction (DEI) document. The Principal Investigator is responsible for all data entered in the EDC and for signing-off at the end of the clinical investigation. The data should be recorded as soon as they are generated.

The person entering data into the database is not allowed to attempt any personal interpretation or to make any decisions on the data other than self-evident corrections as listed in the investigation DEI or data handling report. Single data entry type will be applied. Data required to determine eligibility for the clinical investigation will be collected in the EDC for screening failures.

Data validation /data cleaning procedures are designed to assure validity and accuracy of clinical data. These procedures consist of manual review of clinical data. These procedures consist of manual review performed by the Data Manager and computerized edit checks and queries for identifying data values that are outside the allowed range, incomplete or inconsistent, and CIP deviations. The Data Validation Plan (DVP) specifies the checks that are to be performed on subject data for the clinical investigation. All investigation-specific and standard data validation programming will be tested in a separate testing environment prior to use in the clinical investigation.

When all data from all endpoints of all subjects have been entered, discrepancies solved and reconciliation with the safety database is complete, the database will be locked and the data will be analyzed.

12.1 Data Retention

The medical records of clinical investigation subjects must be retained in accordance with local legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

The PI shall retain all clinical investigation records during the investigation and for the period required by the applicable regulatory requirements or for at least 10 years after the premature termination or completion of the clinical investigation, whichever ever is the longest. The PI must take measures to prevent accidental or premature destruction of these documents. The PI should contact the Sponsor prior to destruction of any records or reports pertaining to the clinical investigation in order to ensure they no longer need to be retained. In addition, if the PI leaves the hospital, he/she should provide the Sponsor with the name and address of the person who will look after and be responsible for the clinical investigation-related records. If the records will be transferred to another person/party, the transfer will be documented at the investigation site or at the Sponsor.

The Sponsor will retain the Study Master File (SMF) in line with applicable regulations or for at least 10 years after the clinical investigation has ended, or, in the event that the device is subsequently placed on the market, at least 10 years after the last device has been placed on the market.

12.2 Monitoring, Audits and Inspections

During the clinical investigation, the monitor will have regular contacts with the investigation site. These contacts will include visits to confirm that the facilities remain adequate to specified standards and that the investigation team is carrying out the procedure stated in the CIP. All data must be accurately recorded in the CRF. Source data verification (SDV), a comparison of data in the CRF with the subject's medical records and other records at the investigation site, will also be performed. The CRF and source documents and records must be made accessible during the monitoring visit.

The monitor or other Sponsor personnel will be available between visits if the PI or other investigation staff at the site needs information and/or advise. Authorized representatives of the Sponsor and/or international Regulatory Agencies / Compentent Authorities may visit the site to perform audits/inspections, including SDV.

13 AMENDMENTS TO THE CIP

Any change to the approved clinical investigation documents will be documented and include a written justification. Any effects of the implemented changes on other clinical investigation documents shall be evaluated and documented. If deemed necessary, affected documents shall be properly updated and relevant parties notified. The version number and date of amendments shall be documented.

All amendments to the CIP will be documented in an amendment log and communicated to relevant parties.

Proposed amendments to the CIP shall be agreed upon between the Sponsor and PI. The amendments to the CIP shall be notified to, or approved by, the IEC and Regulatory Agencies / Competent Authorities, if required.

14 DEVIATIONS FROM THE CIP

A CIP deviation is a failure to follow, intentionally or unintentionally, the requirements of the CIP. Every effort should be made to comply with the requirements of the CIP and the investigator is not allowed to deviate from the CIP. Furthermore, waivers from the CIP is prohibited.

As required by national regulations or guidelines, requests for deviations and reports of deviations will be provided to the IEC if the deviation affects subject's rights, safety and well-being, or the scientific integrity of the clinical investigation.

Under emergency circumstances deviations from the CIP may proceed without prior approval by the Sponsor and favorable opinion of the IEC if the rights, safety and well-being of human subjects need to be protected. Such deviations will be documented and reported to the Sponsor and IEC as soon as possible in accordance with national regulations.

When the monitor or Sponsor identifies that the PI is out of compliance, this will be notified to the PI in writing, with a request to correct the source of the deviation immediately. Corrective action will be implemented to avoid repeated non-compliance, which will usually include re-training and may include terminating the clinical investigation at the site.

The Sponsor is responsible for analyzing deviations and assessing their significance. Corrective action(s) will be implemented to avoid repeated deviations, which may include suspending the clinical investigation at the investigation site or disqualify the PI.

15 DEVICE ACCOUNTABILITY

The investigational device will be shipped to the site or be delivered by a sponsor representative, as applicable, and kept in a locked area. The sponsor will keep records of the shipped investigational devices. A device accountability log will be held on site.
At the investigation close-out visit, a sponsor representative will collect all remaining unused investigational devices. All unused investigational devices will be returned to the sponsor when treatment of the last subject has been completed.
The monitor will verify the accountability process during the site monitoring visits.

16 STATEMENTS OF COMPLIANCE

This clinical investigation will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (Appendix C). Furthermore, the clinical investigation will be conducted in compliance with ISO 14155:2020 and applicable regional or national regulations.

16.1 Institutional Ethics Review

The final CIP, including the final versions of the ICF, must be approved or given a favorable opinion in writing by an IEC and Regulatory Agency / Competent Authority before enrolment of any subject into the clinical investigation. The PI is responsible for informing the IEC of any amendment to the CIP as per local requirements.

Any additional requirements imposed by the IEC or Regulatory Agency / Competent Authority shall be followed.

16.2 Insurance

The Sponsor will be responsible for ensuring adequate insurance covering any injuries to the subject caused by the investigational medical device.

17 INFORMED CONSENT PROCESS

All subjects, and if pediatric subject also their legal representatives, will receive written and verbal information regarding the clinical investigation prior to any investigation-related procedures take place. This information will emphasize that participation in the clinical investigation is voluntary and that the subject may withdraw from the investigation at any time and for any reason. All subjects will be given the opportunity to ask questions about the investigation and will be given sufficient time to decide whether to participate in the investigation or not. If any new important information arise during the clinical investigation the subject will be informed both orally and in writing.

The written subject information explains that the data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation, and that authorized representatives of the Sponsor, international Regulatory Agencies / Competent Authorities or IECs may require direct access to those parts of the medical records relevant to the investigation, including medical history, for verification of data. Additionally, the written subject information specifies that data will be recorded, collected, processed and may be transferred (to either European Economic Area (EEA) countries and / or non-EEA countries). In accordance with the General Data Protection Regulation (GDPR) 2016/679, the data will not identify any subjects taking part in the investigation.

Before any investigation-related procedures, the informed consent will be signed and dated by the subject (and/or legal representative if pediatric subjects), and by the Investigator who gave the verbal and written information. If the subject is 15 years or older he/she should also give written consent, in addition to the legal representative(s) written consent. If a subject younger than 15, who understands the procedures of the investigation, do not want to participate in the investigation, this decision must be respected.

The only exception to the above procedure is if a pediatric subject has more than one legal representative and not all legal representatives are present at the investigation site at the time for consent. The additional legal representative will receive verbal information about the investigation through the phone, and will give oral consent prior to any investigation-related procedures. It will be documented in the subject's medical record that verbal information has been given to the additional legal representative. The legal representative not present at site should have had time to ask questions and think through the decision before giving oral consent. Signed consent will be given as soon as possible thereafter, sent in to the site as soon as possible.

18 ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES

The definitions and procedures for reporting Adverse Events (AE), Adverse Device Effects (ADE), Serious Adverse Events (SAE), Serious Adverse Device Effects (SADE) and Unanticipated Serious Adverse Device Effects (USADE) are presented in the subsections below. It is of utmost importance that all staff involved in the investigation is familiar with the definitions and procedures and it is the responsibility of the Principal Investigator to ensure this.

18.1 Definitions

The following definitions are as per ISO 14155:2020.

Adverse Device Effect (ADE)
Adverse event related to the use of an investigational medical device.

Note 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

Note 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Note 3: This uncludes 'comparator' if the comparator is a medical device.

Adverse Event (AE)
Untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated.

Note 1: This definition includes events related to the investigational medical device or the comparator.

Note 2: This definition includes events related to the procedures involved.

Note 3: For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators.

Device Deficiency
Inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

Note 1: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling.

Note 2: This definition includes device deficiencies related to the investigational medical device or the comparator.

Serious Adverse Device Effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Serious Adverse Event (SAE)
Adverse event that led to any of the following:

a) death,
b) serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:
    i. A life-threatening illness or injury, or
    ii. A permanent impairment of a body structure or a body function including chronic diseases, or
    iii. In-patient or prolonged hospitalization, or
    iv. medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function,
c) foetal distress, foetal death, a congenital abnormality, or birth defect including physical or mental impairment.

Note: Planned hospitalization for pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

Serious health threat
Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons.

Note: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

Unanticipated Serious Adverse Device Effect (USADE)
Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment.

Note: Anticipated Serious Adverse Device Effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.

18.2 Non-reportable adverse events

Not applicable.

18.3 Methods for discovering and documenting AE/ADE

All subjects will be carefully monitored for the occurrence of AEs throughout the clinical investigation, from the first day to the completion of follow up. Events prior to inclusion will be considered medical history. The Principal Investigator will collect safety information using non-leading questions such as "have you experienced any new health problems or worsening of existing conditions?". Events directly observed or spontaneously volunteered by subjects will also be recorded throughout the clinical investigation.

Clearly related signs, symptoms and abnormal diagnostic procedure results should be grouped together and reported as a single diagnosis or syndrome whenever possible.

All AEs, including but not limited to events reported by the subject or reported in response to an open question by the Principal Investigator or member of the investigation team, which fall into any of the previously defined definitions must be recorded as an AE in the CRF and should include the following information:

- Brief description of the event (diagnosis)
- Date of event onset (and time, if relevant)
- Date of event resolution (and time, if relevant)
- Severity
- Seriousness
- Causality assessment (i.e. relationship to medical device and/or procedure)
- Event treatment
- Event outcome / resolution

If the AE meets the seriousness criteria it should be subject to expedited reporting as described in 18.5.

18.3.1 Severity

Severity describes the intensity of an AE and will be assessed as:

1) Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2) Moderate: minimal, local or non-invasive intervention indicated, limiting age-appropriate instrumental activities of daily living.
3) Severe or medically significant but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living.
4) Life-threatening consequences; urgent intervention indicated.
5) Death related to AE.

If an AE changes in severity, it should be reported as an AE of new severity but with the same description and identifier.

18.3.2 Causality

Causality is the relationship between the use of the medical device (including the investigational device, the comparator and the medical – surgical procedure) and the occurrence of each AE.

During the causality assessment, clinical judgment shall be used and the relevant documents, such as the IB, the CIP or the risk analysis report shall be consulted, as all the foreseeable SAEs and the potential risks are listed and assessed there. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered.

For the purpose of harmonizing reports, each SAE will be classified according to four different levels of causality. The Sponsor and the Principal Investigator will use the following definitions to assess the relationship of the SAE to the investigational medical device, the comparator, or the medical – surgical procedures:

- **Not related:** relationship to the device or procedures can be excluded when:
  - The event has no temporal relationship with the use of the investigational device or the procedures related to the investigational device;
  - The serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
  - The discontinuation of medical device application or the reduction of the levels of activation/exposure – when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
  - The event involves a body-site or an organ than cannot be affected by the device or procedure;
  - The serious event can be attributed to another cause (e.g. an underlying or concurrent illness/clinical condition, an effect of another device, drug, treatment or other risk factors);
  - The event does not depend on a false result given by the investigational device used for diagnosis, when applicable;

  In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
- **Possible:** the relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
- **Probable:** the relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot bereasonably be explained by another cause.
- **Causal relationship:** the serious event is associated with the investigational device, comparator or with procedures beyond reasonable doubt when:
  - The event is known side effect of the product category the device belongs to or of similar devices and procedures;
  - The event has a temporal relationship with investigational device use/application or procedures;
  - The event involved a body-site or organ that:
    - The investigational device or procedures are applied to;
    - The investigational device or procedures have an effect on;
  - The serious event follows a known response pattern to the medical device (if the response pattern is previously known);
  - The discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of activation/exposure), impact on the serious event (when clinically feasible);
  - Other possible causes (e.g. an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
  - Harm to the subject is due to error in use;
  - The event depends on a false result given by the investigational device used for diagnosis, when applicable;

  In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

The Sponsor and the Principal Investigator will distinguish between AEs related to the investigational device, the comparator and those related to the procedures (any procedure

specific to the clinical investigation). An AE can be related to both the procedures and the device. Complications of procedures are considered not related if the said procedures would have been applied to the subjects also in the absence of device use/application.

Particular attention shall be given to the causality evaluation of USADE, since the occurrence of USADE could suggest that the clinical investigation places subjects at increased risk of harm than was expected beforehand.

In case of disagreement between the Sponsor and the Principal Investigator assessments of the AE, both opinions shall be communicated to concerned parties.

18.4 Methods for Discovering and Documenting Device Deficiencies

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance shall be reported as a device deficiency without unnecessary delay to the Sponsor by using the device deficiency form. It is the Principal Investigator's responsibility to record every observed device deficiency together with an assessment. The Sponsor shall review all device deficiencies and determine and document in writing whether they could have led to a SADE. Device deficiencies that are assessed to or have SADE potential should be subjected to expedited reporting as described in section 18.5.

18.5 Reporting of SAE/SADE and Device Deficiencies with SADE potential

MDR 2017/745

The following events are considered reportable events according to Regulation (EU) 2017/745:

- Any SAE that has a causal relationship with the investigational device, the comarator or the investigation procedure or where such causal relationship is reasonably possible;
- Any device deficiency that might have led to a SAE if:
  - Suitable action had not been taken or
  - Intervention had not been made or
  - If circumstances had been less fortunate
- New findings/updates in relation to already reported events.

SAEs/SADEs and device deficiencies with with SADE potential must be reported to the Sponsor immediately, but **not later than 3 calendar days after investigational site investigation personnel's awareness of the event**, regardless of the time that may have elapsed from the time the event occurred.

The initial report should contain as much information as possible, but as a minimum the following information:

- Subject ID
- SAE ID
- Date of procedure/first use
- Date of event onset
- SAE or DD
- Age (years)
- Patient gender (female, male, other, unknown)

- Classification of event:
  - death,
  - life-threatening illness or injury,
  - permanent impairment/chronic disease,
  - hospitalization,
  - medical or surgical intervention,
  - foetal distress, foetal death or congenital physical or mental or birth defect,
  - not applicable[1]
- Description of event:
  - Nature of the observed symptoms
  - Duration and severity of the symptoms
  - Date of onset of first signs of the event (before it became a SAE)
  - Medical background of the patient
  - Medical care of the patient
  - Comments on the event in relation to already known safety data
- Action/treatment/outcome
- Relationship to procedure (not related, possible, probable, causal)
- Relationship to the device (not related, possible, probable, causal)
- Unanticipated SADE (Yes, No)
- Investigation arm (test group, comparison group, blinded, not applicable)
- Event status (resolved, resolved with sequelae, ongoing, death)
- Date of event resolution (if ongoing enter not applicable)

The Sponsor must also promptly receive a completed report. All SAEs have to be reported whether or not they are considered causally related to the investigational medical device, comparator or medical – surgical procedure.

SAE/SADE EMERGENCY CONTACT DETAILS
Name: Mattias Andrup
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Email: mattias.andrup@circiuspharma.com

Since this is a post-market clinical investigation all SAEs will be handled according to the Sponsors vigilance system and in accordance with MDR and the vigilance provisions laid down in Article 87 to 90 and in the acts adopted pursuant to Article 91. However, for the SAEs where a causal relationship between the SAE and the preceding investigational procedure has been established the reporting procedures of clinical investigations as outlined in Article 80 shall be followed; the event must be reported to the Regulatory Agencies / Competent Authorities and ECs, where the PMCF investigation has commenced. The period for reporting shall take account of the severity of the event. Where necessary to ensure timely reporting, the Sponsor may submit an initial report that is incomplete followed by a complete report. The Sponsor should inform the IEC and Regulatory Agencies / Competent Authorities about reportable events through EUDAMED (once established) or as per local requirements.

[1] This option is only to be selected in case of reportable device deficiencies that did not lead to an SAE.

18.6 Foreseeable adverse events and anticipated adverse device effects

There are few and mild side-effects reported with regards to the use of Otinova® Ear Spray, such as the possibility of temporary mild irritation or stinging in the ear canal. Small amounts of salt precipitation in the outer ear canal can occur.

18.7 Data Monitoring Committee

Establishment of a Data Monitoring Committee (DMC) is not considered necessary for this post-market clinical investigation as 1) there will be only one investigational site, well-experienced in clinical investigations and 2) the benefit-risk profile of the investigational devices do not indicate a need for a DMC. In case data retrieved during the clinical investigation contradicts this decision, it will be reconsidered.

19 Vulnerable Population

In this clinical investigation, pediatric subjects from the age of 5 will participate. Pediatric subjects are per se described as a vulnerable population according to ISO 14155:2020. Therefore, also the potential subjects' legal representatives will receive information both verbally and written about the study prior any decision about the subjects' participation. If not all legal representative(s) are present at the time of consent, the additional legal representative(s) will receive oral information about the investigation and give oral consent. Written consent will take place as soon as possible thereafter. Both the potential subject and the legal representative(s) need to voluntarily agree to participate. The subject will be informed about the clinical investigation within his/her ability to understand, i.e. additional versions of the subject information have been developed to target different ages. If the subject will have specific difficulties to understand the contents of participating in the clinical investigation, i.e. as a child may have, additional time will be given for questions regarding the investigation as well as consent procedure. For more information on the consent process for pediatric subjects, see Section 17.

20 SUSPENSION OR EARLY TERMINATION OF CLINICAL INVESTIGATION

If the clinical investigation is terminated early or suspended due to reasons of safety, the Sponsor will promptly inform the PI(s) and the investigation site(s) of the termination or suspension and the reason(s) thereof. The IEC will also be informed promptly and provided with the reason(s) for the termination or suspension by the Sponsor or by the PI(s) / investigation site(s).

In addition, CIP violations may result in termination of the Clinical Investigation at a site.
CIP violations are deviations made without permission as a result of error or fraud/misconduct. Where the monitor or Sponsor identifies that the PI is out of compliance, this will be noted to the PI in writing, with a request to correct the source of the deviation immediately. Corrective actions will be implemented to avoid repeated non-compliance, including re-training. However, in case of repeated non-compliance despite implemented corrective actions, the clinical investigation will be terminated at the site.

20.1 Subject Follow-up

If the clinical investigation is prematurely terminated, the Sponsor and the PI(s) will assure that adequate consideration is given to the protection of subjects' interest, including subject follow-up.

21 PUBLICATION POLICY

The clinical investigation will be registered in a publicly accessible database before recruitment of the first subject.

A final report of the clinical investigation (CIR) will be completed, even if the investigation is prematurely terminated. The report will be prepared by the Sponsor according to the guideline presented in Annex D of ISO 14155:2020.

All publications and presentations must be based upon the CIR.

All information supplied by the Sponsor in connection with this investigation will remain the sole property of the Sponsor and is to be considered confidential information. No confidential information will be disclosed to others without obtaining prior written consent from the Sponsor and will not be used except in the conduct of this investigation.

The Sponsor may choose to publish or present data from this clinical investigation. If a PI is offered first authorship, he/she will be asked to comment and approve the publication. The Sponsor has the right to use the results for registration and internal presentation and for promotion.

22 REFERENCES

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18. Otinova. Risk Management Report. RISK-4483. Version 1. 2020-11-17.

23 APPENDICES

23.1 Appendix A – Clinical Investigation Plan Agreement Form

Investigation code: CIR_001

CIP version: C, 09-May-2023

I agree to the terms of this CIP. I will conduct the investigation according to the procedures specified herein.

Site No: 01

Principal Investigator

Name: Cristina Ioanes

Signature: _____

Date (dd-Mmm-yyyy): _____

Investigation code: CIR_001

CIP version: C, 09-May-2023

I agree to the terms of this CIP. I will conduct the investigation according to the procedures specified herein.

Site No: 02

Principal Investigator

Name: Daniel Wilhelms

Signature: _____

Date (dd-Mmm-yyyy): _____

Investigation code: CIR_001

CIP version: C, 09-May-2023

I agree to the terms of this CIP. I will conduct the investigation according to the procedures specified herein.

Site No: 03

Principal Investigator

Name: Sarah Maleki

Signature: _____

Date (dd-Mmm-yyyy): _____

23.2 Appendix B – Clinical Investigation Contact List

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23.3 Appendix C – Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington, DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

PREAMBLE

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

GENERAL PRINCIPLES

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
5. Medical progress is based on research that ultimately must include studies involving human subjects.
6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.
8. While the primary purpose of medical research is to generate new knowledge, this goal can

never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.
10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.
11. Medical research should be conducted in a manner that minimises possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

RISKS, BURDENS AND BENEFITS

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

VULNERABLE GROUPS AND INDIVIDUALS

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research

SCIENTIFIC REQUIREMENTS AND RESEARCH PROTOCOLS

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions

RESEARCH ETHICS COMMITTEES

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

PRIVACY AND CONFIDENTIALITY

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

INFORMED CONSENT

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.
26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.
28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.
29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.
30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed,

the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.
32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

USE OF PLACEBO

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option

POST-TRIAL PROVISIONS

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

RESEARCH REGISTRATION AND PUBLICATIONS AND DISSEMINATION OF RESULTS

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.
36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be

published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

UNPROVEN INTERVENTIONS IN CLINICAL PRACTICE

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.