First-in-human, placebo-controlled, ascending dose study to assess the safety, tolerability and pharmacokinetics of a single intratympanic injection of AC102 in healthy volunteers

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The primary objective of this study is: * To assess the safety and tolerability of single ascending volumes of placebo as well as volumes and doses of AC102-suspension by intratympanic injection in healthy male and female subjects.The secondary...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Hearing disorders
Study type	Interventional

Summary

ID

NL-OMON55334

Source
ToetsingOnline

Brief title
Niet van toepassing

Condition

- Hearing disorders

Synonym
hearing impairment, now healty volunteers), tinnitus (at a later stage

Research involving
Human

Sponsors and support

Primary sponsor: AudioCure Pharma GmbH
Source(s) of monetary or material Support: Farmacceutische industrie

Intervention

Keyword: First in Man, Healthy volunteers, Study drug intended to later treat patients with hearing loss

Outcome measures

Primary outcome

Safety Endpoints:

* Treatment-emergent (serious) adverse events (TE(S)AEs)

* Treatment emergent adverse events of special interest (AESIs):

o Permanent sensorineural hearing loss

o Persistent conductive hearing loss

o Persistent tinnitus

o Persistent vestibular vertigo

o Persistent tympanic membrane perforation

o Infections of the outer, middle and inner ear

* Concomitant medication

* Clinical laboratory tests:

o Hematology

o Biochemistry

o Urinalysis

* Vital signs:

o Pulse rate (bpm)

o Systolic and diastolic blood pressure (mmHg)

o Body temperature

* ECG:

o Heart rate (HR) (beats per minute [bpm]), QTcF

Pharmacokinetic endpoints:

The following endpoints will be determined for AC102 by non-compartmental analysis of the plasma concentration-time data:

* The area under the plasma concentration-time curve from zero to infinity (AUC0-inf)

* The maximum plasma concentration (Cmax)

* The area under the plasma concentration-time curve from zero to t of the last measured concentration above the limit of quantification (AUC0-last)

* The time to reach maximum plasma concentration (tmax)

* The terminal disposition rate constant (*z) with the respective half-life (t*)

* Other parameters, including apparent volume of distribution (Vz/F), apparent total body clearance (CL/F), and other parameters as appropriate and possible, as well as dose adjusted parameters, may be determined.

Secondary outcome

Not applicable

Study description

Background summary

AudioCure Pharma GmbH develops AC102 (6-fluoro-9-methyl-9H-pyrido[3,4-b]-indole) as novel pharmaceutical therapy for the prevention and treatment of a range of hearing impairments with high unmet medical need. The proposed clinical trial will be the first clinical

investigation with this new chemical entity and be performed in healthy volunteers to be able to detect possible adverse effects that might be masked by disease specific symptoms in patients.
The current focus of AudioCure*s development program for AC102 is on acute hearing loss. Despite numerous efforts, to date, there are no approved pharmacotherapies available for the treatment of Sudden Sensorineural Hearing Loss (SSNHL). The treatment of hearing loss with systemic glucocorticoids, which have anti-inflammatory and immunosuppressive properties, is recommended in many countries. However, there is a lack of clear evidence for significant beneficial effects of glucocorticoids therapy. Furthermore, such treatment might not be justified due to the numerous possible side effects (e.g. hypertension, osteoporosis, behavioral disturbances, diabetes).
The characteristic pathological feature of SSNHL is damage to the hair cells, the sensory cells of the cochlea (located in the inner ear), and / or the spiral ganglion neurons (SGNs) that comprise the auditory nerve. Inner and outer hair cells are responsible for signal amplification and the conversion of the acoustic stimulus into a neuronal signal that is transmitted by the afferent SGNs to the central auditory system. Hair cells are the most vulnerable elements in the cochlea. A crucial aspect of SSNHL is that neither the hair cells nor the SGNs can be replaced once they are lost. Therefore, an effective treatment of SSNHL requires fast and target-specific intervention in order to avoid the acute hearing loss becoming a permanent condition (Raphael et al., 2002).
The inner ear and the SGNs are well protected areas within the body and cannot be reached easily by a systemically administered medication as it would have to pass the blood-inner ear barrier and the blood-brain barrier. These barriers prevent systemically taken drugs (e.g. orally) from reaching the inner ear at concentrations sufficient to have a therapeutic effect. Increasing the dose systemically to reach sufficient inner ear exposure may cause or enhance systemic adverse reactions. To avoid this, drugs have to be delivered locally into the middle ear by e.g. intratympanic (through the ear drum) injection. From the middle ear, the drug can diffuse across the round window membrane (RWM) into the inner ear. Intratympanic injections represent a routine outpatient procedure for otolaryngologists.

Study objective

The primary objective of this study is:
* To assess the safety and tolerability of single ascending volumes of placebo as well as volumes and doses of AC102-suspension by intratympanic injection in healthy male and female subjects.
The secondary objectives of this study are:
* To determine single dose pharmacokinetics of intratympanically injected AC102 in healthy male and female subjects.

Study design

This is a multi center, open label, placebo-controlled, single dose escalating study.
Each cohort will receive a single dose of placebo or AC102-suspension in an ascending order.
Volume and/or dose escalation will only proceed following satisfactory review of all available safety data.
Approximately up to 16 single-dose cohorts are planned (C1 to C12, n=3 subjects per cohort). For the first (C1) and the fifth (C5) single-dose cohort, sentinel dosing of 1 subject will occur approximately 2 weeks before dosing the remaining 2 subjects.
The different cohorts may overlap, but always will a volume be evaluated first using placebo only. It may be needed to pause escalation or to add another cohort to confirm safety/tolerability data. The last cohort will be used to repeat and confirm the optimal volume (= selected volume) and dose that were selected based on the evaluation of all previous cohorts (safety/tolerability and practicability of administration). Escalation steps and adaptations to the proposed dosing regimen will be submitted for approval.

Intervention

Single intratympanic injection with study medication

Study burden and risks

Total of max. 6 visits, 2 days in hospital, blood draws, hearing tests, a single injection in one ear, lifestyle restrictions.
The injection can be painful, a sense of pressure in the ear can be felt for a short time, the volume of the injection can cause a temporary partial hearing loss, vertigo that will pass quickly might occur, a small scar might remain in the tympanum but this will not lead to hearing loss.
There is a very small chance on permanent perforation of the tympanum, a very small chance on permanent hearing loss, a very small chance of damage to the nerve affecting the sense of taste

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Signed Institutional Review Board (IRB) / Independent Ethics Committee (IEC) approved informed consent form (ICF)
2. Willing and able to attend the trial visits
3. Able to read and understand trial documents and follow Investigator and trial personnel instructions during visits, including audiology measurements
4. Female or male
5. Age * 18 years and * 40 years at the day of Screening
6. Body mass index (BMI) 18.0 - 30.0 kg/m2, inclusive, where BMI (kg/m2) <= body weight (kg) / height2*(m2) at Screening Visit
7. Healthy as judged by a responsible physician with no clinically significant abnormality identified on the medical or laboratory evaluation, including 12-lead ECG, vital sign assessment or physical examination
8. Normal age-related hearing in both ears according to DIN EN ISO 8253-1 and DIN 7029:2017
9. Willing and able to use adequate hearing protection and to refrain from engaging in activities or work involving loud noise exposure where sufficient hearing protection is not possible or ensured for the duration of their participation in this study
10. Willing and able to protect the ear canal and middle ear from water exposure for as long as the tympanic membrane is not fully closed
11. A female volunteer must meet one of the following criteria:
* If of childbearing potential * agrees to use one of the accepted contraceptive regimens from at least 28 days prior to until at least 30 days after study medication administration. An acceptable method of contraception

includes at least one of the following:
a. Abstinence from heterosexual intercourse
b. Combined (contains estrogen and progestogen) hormonal contraception (oral, vaginal, transdermal)
c. Progestogen only contraception (oral, injectable, implantable)
d. Intrauterine device
e. Intrauterine hormone-releasing system
f. Bilateral tubal ligation
g. Vasectomized partner
* If of non-childbearing potential * should be surgically sterile (i.e. has undergone complete hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or in a postmenopausal state (at least one year without menses at Screening)
12. A male volunteer with sexual partners who are pregnant, possibly pregnant, or who could become pregnant must meet the following criteria:
* Subject is unable to procreate, defined as surgically sterile (i.e. has undergone a vasectomy at last 6 months before Screening)
* Subject agrees to use one of the accepted contraceptive regimens until 90 days after study medication administration. An acceptable method of contraception includes one of the following:
a. Abstinence from heterosexual intercourse
b. Condom with spermicide.

Exclusion criteria

1. History of acute hearing loss from noise trauma, barotrauma or head trauma in either ear at any time
2. History of idiopathic sudden sensorineural hearing loss in the past 2 years
3. Congenital hearing loss
4. History of chronic (> 6 months) noise exposure (for leisure or profession)
5. Chronic or acute tinnitus in either ear
6. Current vertigo/previous balance or vestibular disorders
7. Any clinically significant external or middle-ear pathology observed by otoscopic examination or tympanometry (i.e. reduced mobility of the tympanic membrane)
8. Any clinically significant abnormality of the tympanic membrane or the outer ear canal in the selected ear that would preclude intratympanic administration
9. Absence of detectable OAEs in the frequency band with a concomitant clinically significant increase in hearing thresholds in accordance with DIN EN ISO 8253-1 and DIN 7029:2017
10. Known family history of hearing impairment, other than age related
11. History of autoimmune hearing loss, radiation-induced hearing loss, fluctuating hearing, endolymphatic hydrops or Menière*s disease in either ear
12. History of chronic inflammatory or suppurative ear disease or cholesteatoma
13. Current evidence or history of acoustic neuroma or other retrocochlear

damage
14. History of otosclerosis
15. Suspected perilymph fistula or membrane rupture in either ear
16. Otitis media or otitis externa that is ongoing or ended within 30 days prior to study treatment or is occurring several times per year
17. Radiation therapy in the head and neck area
18. Any therapy known as ototoxic (e.g. aminoglycosides [systemic or ototopical], cisplatin, loop diuretics, quinine etc.)
19. Taking any anti-coagulant medication (direct oral anticoagulant [DOAC], e.g. Apixaban®), vitamin K antagonists (e.g. Marcumar®), thrombocyte aggregation blockers (e.g. Aspirin®) chronically or Aspirin® as a pain killer acutely within one week before treatment
20. History or presence of drug abuse or alcoholism within the past 2 years
21. Positive urine screen of drugs of abuse (if not due to concomitant medication, e.g. benzodiazepines as hypnotics) or alcohol breath test at Screening or Day -1
22. Ingestion of alcohol within 48 hours prior to study medication administration and during the in-house period.
23. Current smokers
24. Excess in xanthine consumption (more than 5 cups of coffee/day or equivalent)
25. Subjects with diagnosed anxiety disorders, psychosis, depression, schizophrenia, attempted suicide or other significant psychiatric conditions that can impact their ability to cooperate and comply with the study protocol
26. Any clinically relevant autoimmune, respiratory, cardiovascular, hepatic, gastrointestinal, renal, dermatological, neurological or other abnormality that in the opinion of the Investigator may pose a safety risk to a subject in this study, which may confound safety assessment, or may interfere with study participation or the evaluation of study treatment
27. Known human immunodeficiency virus (HIV), hepatitis B or hepatitis C infection
28. Having an active infection with SARS-CoV-2
29. Abnormal and clinically relevant laboratory results
30. Systemic steroids within the last three months (topical steroids like nasal spray or cremes are allowed)
31. Seated pulse rate less than 45 beats per minute (bpm) or more than 100 bpm at Screening or Day -1
32. Seated blood pressure below 95/55 mmHg at Screening or Day -1
33. Seated blood pressure higher than 150/90 mmHg at Screening or Day -1 (measurement may be repeated in 15 minutes if initial reading is believed to be atypical for the subject)
34. Known congenital long QT syndrome or a corrected QT interval (QTc) using Fridericia correction (QTcF) at Screening (QTcF > 450 msec for males and > 470 msec for females) or other clinically significant ECG abnormalities
35. Concurrent participation in another clinical study or participation in another clinical study within 30 days or 5 half-lives of the experimental drug (whichever is longer) prior to Screening Visit

36. Donation or loss of more than 450 mL blood during the 3 months before the start of Screening
37. Women who are breast feeding, pregnant or plan to become pregnant during the study or women of childbearing potential who are unwilling or unable to practice an effective method of contraception
38. Subjects who are involved in the organization of the clinical investigation or are in any way dependent on the Investigator or Sponsor
39. Major surgery within eight weeks before Screening or scheduled/planned surgery within the time frame of the study
40. Legal incapacity or limited legal capacity.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	21-07-2020
Enrollment:	42
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	AC102
Generic name:	AC102

Ethics review

Approved WMO Date:	02-06-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-06-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-07-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-07-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-09-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-10-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-11-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	26-11-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-12-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-12-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-01-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-02-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2019-004969-40-NL
CCMO	NL72516.056.20