Efficacy of AM 101 in Patients with Acute Inner Ear Tinnitus: A Multi-Centre, Double-Blind, Randomised, Placebo-Controlled, Multiple Dose, Group Comparison Phase II Study

Published: 04-03-2009
Last updated: 05-05-2024

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

Summary

ID

NL-OMON33296

Source
ToetsingOnline

Brief title
Treatment of acute inner ear tinnitus

Condition

- Hearing disorders

Synonym
tinnitus

Research involving
Human

Sponsors and support

Primary sponsor: Auris Medical AG
Source(s) of monetary or material Support: Auris Medical

Intervention

Keyword: ketamine, NMDA receptor antagonist, Tinnitus

Outcome measures

Primary outcome

The primary efficacy outcome is the change in the minimum masking level (MML)

from Baseline to D90.

Secondary outcome

Secondary efficacy endpoints

• The change in the minimum masking level (MML) from Baseline to D7 and D30

• The change in tinnitus loudness by loudness matching from Baseline to D7,

D30, and D90.

• Global impression of change questionnaire for tinnitus severity at study

completion (D90)

• The change in tinnitus annoyance by magnitude estimation from baseline to D7,

D30, and D90

• The change in tinnitus loudness by magnitude estimation from baseline to D7,

D30, and D90.

• The change in tinnitus handicap from baseline as measured by the TBF-12

questionnaire at D90

• The change in sleep impact by magnitude estimation from baseline to D90

Study description

Background summary

Efficacy of AM 101 in Patients with Acute Inner Ear Tinnitus: A Multi-Centre, Double-Blind, Randomised, Placebo-Controlled, Multiple Dose, Group Comparison Phase II Study

Study objective

Primary objective
The primary objective of the study is the evaluation of the therapeutic benefit of three repeated dose intratympanic AM 101 injections in comparison to placebo in the treatment of persistent acute inner ear tinnitus following acute otitis media, acute acoustic trauma or sudden deafness.
Secondary objectives
The secondary objectives of the study are (a) safety and local tolerance of intratympanically applied AM 101 and (b) identification of the optimal dose of AM 101 in the treatment of persistent acute inner ear tinnitus from acute acoustic trauma or sudden deafness.

Study design

This clinical trial is designed as a multicentre, double-blind, randomised, placebo-controlled, multiple dose, group comparison phase II study.

Intervention

After topical anaesthesia of the tympanic membrane, patients will receive an intratympanic injection of 250 µl of study medication on D0. Following injection they will rest for 30 minutes. On days D1 and D2 the procedure of drug application will be repeated.
Patients will be randomized on D0 to receive either AM 101 270 µg/ml, AM-101 810 µg/ml, or placebo.
In case of bilateral tinnitus, only the ear with the higher tinnitus loudness (as determined by loudness matching at 1 kHz) at baseline will be treated, or, if equally loud, the ear with the greater hearing loss at 4 kHz will be treated.

Study burden and risks

As of today, there exists neither a universal standard of care for tinnitus, nor a truly proven, effective treatment method. Inner ear tinnitus may be short and transitory, however, it may also become permanent and seriously impact the ability to sleep, relax, or to concentrate, or lead to tiredness, irritation,

nervousness, despair, frustration, or depression.
Possible problems, risks for injuries or distress:
The pharmacology of Ketamine and Esketamine the API in AM-101 is well known, and the drug has been in clinical use for a relatively long time already. Ketamine is considered to have a good safety profile.
AM-101 had been tested in humans with intratympanic injection for the treatment of acute inner ear tinnitus before. In the phase I/II clinical trial with AM-101, all 4 doses - 30, 90, 270 and 810 ug/ml - were well tolerated and showed no toxicities. The safety of the triple doses of 270 and 810 µg/ml, which are to be administered in the phase II study, are considered to be safe given the good safety profile observed in the previous clinical trial as well as based on animal toxicology data. Repeated administration of Esketamine by way of a 14 day continuous infusion onto the round window membrane of guinea-pigs showed no toxicities even at 10 mg/ml respectively 2 mg in total dose.
The treatment administration by intratympanic injection is a well established and safe minimally invasive procedure and is usually well tolerated. The small incision cicatrices rapidly. In very rare cases, local bleeding may occur into the middle ear. Further, there may be infections in the middle ear. These complications can be well treated or pass away spontaneously. The first clinical trial with AM-101 confirmed the good safety of intratympanic injections.
Ethical considerations:
It is planned to include a placebo to the control for spontaneous recovery of hearing loss. A placebo design was chosen, as there is no proven standard of care for the treatment of acute inner ear tinnitus. All patients, including the participants receiving placebo (1 out of 3), benefit from close monitoring and extensive medical care within the period of the study. All participants have the opportunity to make a valuable contribution to inner ear tinnitus research.
Potential benefits for the patient
By participating in the phase II clinical trial, patients have a 2 in 3 chance to get access to a new medicinal product and treatment method which may for the first time ever provide effective relief from inner ear tinnitus. The phase I/II clinical trial provided some first indications of potential efficacy of the investigated medicinal product. Furthermore, all patients will get - free of charge - comprehensive and intensive health care by specialists. Their health, and in particular their hearing function, will be closely monitored. Importantly, the provided medical care and attention will tend to decrease the stress commonly related to tinnitus, which is known to potentiate the perception of tinnitus. Thus also patients treated with placebo are likely to benefit from participation in the trial.
Benefit/risk ratio:
The Sponsor considers risk/benefit ratio to be positive. AM-101 poses no significant safety concerns for study participants, and offers at the same time the potential for attenuation or suppression of acute inner ear tinnitus.

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

• Persistent tinnitus following acute acoustic trauma or sudden deafness or acute otitis media with onset less than three months ago (i.e. acute tinnitus)
• Tinnitus provoking incident of acute acoustic trauma or sudden deafness or acute otitis media is documented by medical report
• Minimum Masking Level (MML) of at least 5 dB SL
• Age >= 18 years and <= 65 years
• Negative pregnancy test for women of childbearing potential
• Willing and able to attend the on-study visits
• Written informed consent before participation in the study

Exclusion criteria

• Tinnitus that is not completely maskable
• Fluctuating tinnitus
• Intermittent tinnitus
• Meniere*s Disease
• Acute or chronic otitis media or otitis externa
• Any ongoing therapy known as potentially tinnitus-inducing (e.g. aminoglycosides, cisplatin, loop diuretics, high doses of aspirin, quinine etc.)
• Any drug-based therapy for inner ear hearing loss that is ongoing or was performed in the past 2 weeks, e.g. prednisolone, dexamethasone, pentoxyfilline, betahistine, diazepam, carbamazepine, sodium valproate and antidepressants
• Concomitant use of any other NMDA receptor antagonist (e.g. memantine, dextromethorphan, ifenprodil)
• Any drug-based therapy for acute otitis media that is ongoing or was performed in the past 2 weeks
• Any ongoing or planned concomitant medication for the treatment of tinnitus until 90 days after study drug application
• History or presence of drug abuse or alcoholism
• Any clinically relevant respiratory, cardiovascular, neurological (except vertigo), or psychiatric disorder
• Known hypersensitivity, allergy or intolerance to the study medication or any history of severe abnormal drug reaction
• Women who are breast-feeding, pregnant or who plan a pregnancy during the trial
• Women of childbearing potential who declare being unwilling or unable to practice contraception such as hormonal contraceptives, sexual abstinence or intercourse with a vasectomised partner
• Concurrent participation in another clinical trial with an investigational drug or participation in another clinical trial with an investigational drug within 30 days prior to study entry

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-02-2010
Enrollment:	15
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	S-(+)-ketamine
Generic name:	Esketamine hydrochloride
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	04-03-2009
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	08-06-2009
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	23-06-2009
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	06-10-2009
Application type:	Amendment

Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	01-06-2011
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	07-06-2011
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	EUCTR2008-005178-10-NL
ClinicalTrials.gov	NCTNr.notyetgiven
CCMO	NL26815.068.09