Clinical trial results:
Comparison of Single versus Repeat Doses of AM-101 in the Treatment of Acute Inner Ear Tinnitus (TACTT1)

Summary

EudraCT number	2011-005384-24
Trial protocol	BE DE
Global end of trial date	21 May 2013

Results information

Result version number	v1 (current)
This version publication date	27 July 2016
First version publication date	27 July 2016

Trial information

Trial identification

Sponsor protocol code	AM-101-CL-10-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01270282
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Auris Medical AG
Sponsor organisation address	Falknerstr. 4, Basel, Switzerland, 4001
Public contact	Thomas Meyer, Auris Medical AG, +41 61 201 13 50, ear@aurismedical.com
Scientific contact	Thomas Meyer, Auris Medical AG, +41 61 201 13 50, ear@aurismedical.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 July 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 May 2013
Global end of trial reached?	Yes
Global end of trial date	21 May 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective: The primary objective of the trial was the evaluation of the appropriate dosing regimen for intratympanic (i.t.) AM-101 injections in the treatment of acute inner ear tinnitus. Secondary objectives: The secondary objectives of the trial were (a) the further assessment of the safety and local tolerance of i.t. administered AM-101, and (b) the further evaluation of AM-101's biodistribution.

Protection of trial subjects:

This Clinical Trial was conducted in accordance with the study protocol, the International Conference on Harmonisation (ICH) harmonized tripartite guideline on Good Clinical Practices (GCP) (E6), as well as Food and Drug Administration (FDA) regulations for investigational new drugs outlined in 21 CFR, Section 312, 50 and 56, and the ethical principles outlined in the Declaration of Helsinki dated 1989 (US sites), respectively in their most current version.

Background therapy:

N/A

Evidence for comparator:

N/A

Actual start date of recruitment	09 February 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 39
Country: Number of subjects enrolled	Germany: 15
Country: Number of subjects enrolled	Belgium: 15
Country: Number of subjects enrolled	Poland: 16
Worldwide total number of subjects	85
EEA total number of subjects	46

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	85
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a Phase IIa, randomised, multi centre, double-blind, placebo-controlled dose-finding, efficacy, tolerability, safety, and pharmacokinetic study of AM-101 in the treatment of subjects with acute inner ear tinnitus (6 US and 9 EU sites). Eligible subjects were to have an onset of tinnitus no longer than 3 months prior to study start.

Pre-assignment

Screening details:

Main inclusion criteria were: Persistent tinnitus (unilateral or bilateral) following AAT, acute OM, middle ear surgery or inner ear barotrauma with onset up to 3 months ago, documented by medical report; Age from 18 - 65 years.

A total of 87 patients were screened. Of these, 85 were randomised.

Period 1

Period 1 title	Whole study period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

The Sponsor, Investigators as well as the subjects were blinded regarding the dose administered during the study. In particular, the gel formulation was of the same appearance for AM-101 than the Placebo and revealed no differences during or following injection, neither to the Investigator, nor to the subject.

Arms

Are arms mutually exclusive?	Yes
Arm title	AM-101 0.81 mg/mL gel (single)

Arm description:

Single intratympanic administration of AM-101 0.81 mg/mL gel at D0

Arm type	Experimental
Investigational medicinal product name	Esketamine hydrochloride gel
Investigational medicinal product code	AM-101
Other name	
Pharmaceutical forms	Gel for injection
Routes of administration	Intratympanic use

Dosage and administration details:

Single intratympanic administration of AM-101 0.81 mg/mL (0.25 mL). In case of bilateral tinnitus, both ears were treated.

Arm title	Placebo (single)

Arm description:

Single intratympanic administration of placebo gel at D0.

Arm type	Placebo
Investigational medicinal product name	Placebo gel
Investigational medicinal product code	Placebo
Other name	
Pharmaceutical forms	Gel for injection
Routes of administration	Intratympanic use

Dosage and administration details:

Single intratympanic administration of AM-101 0 mg/mL (0.25 mL). In case of bilateral tinnitus, both ears were treated.

Arm title	AM-101 0.81 mg/mL gel (triple)

Arm description:

Triple intratympanic administration over 2 weeks of AM-101 0.81 mg/mL gel at D0, D7, D14

Arm type	Experimental
Investigational medicinal product name	Esketamine hydrochloride gel
Investigational medicinal product code	AM-101
Other name	
Pharmaceutical forms	Gel for injection
Routes of administration	Intratympanic use

Dosage and administration details:

Triple intratympanic administration of AM-101 0.81 mg/mL (0.25 mL). In case of bilateral tinnitus, both ears were treated.

Arm title	Placebo (triple)

Arm description:

Triple intratympanic administration over 2 weeks of placebo gel at D0, D7, D14

Arm type	Placebo
Investigational medicinal product name	Placebo gel
Investigational medicinal product code	Placebo
Other name	
Pharmaceutical forms	Gel for injection
Routes of administration	Intratympanic use

Dosage and administration details:

Triple intratympanic administration of AM-101 0 mg/mL (0.25 mL). In case of bilateral tinnitus, both ears were treated.

Number of subjects in period 1	AM-101 0.81 mg/mL gel (single)	Placebo (single)	AM-101 0.81 mg/mL gel (triple)
Started	33	14	25
Completed	27	14	22
Not completed	6	0	3
Consent withdrawn by subject	3	-	2
Significant medical condition	-	-	1
Lost to follow-up	2	-	-
Not treated, consent withdrawn before dosing	1	-	-

Number of subjects in period 1	Placebo (triple)
Started	13
Completed	10
Not completed	3
Consent withdrawn by subject	1
Significant medical condition	-
Lost to follow-up	2
Not treated, consent withdrawn before dosing	-

Baseline characteristics

Reporting groups	
Reporting group title	AM-101 0.81 mg/mL gel (single)
Reporting group description:	
Single intratympanic administration of AM-101 0.81 mg/mL gel at D0	
Reporting group title	Placebo (single)
Reporting group description:	
Single intratympanic administration of placebo gel at D0.	
Reporting group title	AM-101 0.81 mg/mL gel (triple)
Reporting group description:	
Triple intratympanic administration over 2 weeks of AM-101 0.81 mg/mL gel at D0, D7, D14	
Reporting group title	Placebo (triple)
Reporting group description:	
Triple intratympanic administration over 2 weeks of placebo gel at D0, D7, D14	

Reporting group values	AM-101 0.81 mg/mL gel (single)	Placebo (single)	AM-101 0.81 mg/mL gel (triple)
Number of subjects	33	14	25
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	33	14	25
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	38.2	41	40.6
standard deviation	± 12.42	± 10.36	± 13.03
Gender categorical Units: Subjects			
Female	10	2	8
Male	23	12	17
Ethnic group Units: Subjects			
Caucasian	32	13	25
African	0	0	0
Asian	0	0	0
Hispanic	1	1	0

Reporting group values	Placebo (triple)	Total	
Number of subjects	13	85	

Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	13	85	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	40.4		
standard deviation	± 12.72	-	
Gender categorical Units: Subjects			
Female	4	24	
Male	9	61	
Ethnic group Units: Subjects			
Caucasian	13	83	
African	0	0	
Asian	0	0	
Hispanic	0	2	

Subject analysis sets

Subject analysis set title	Valid for Efficacy
Subject analysis set type	Per protocol

Subject analysis set description:

Major protocol violators have been excluded. 66 subjects were included in the Valid for Efficacy set (VfE), of whom
44 received AM-101 and 22 Placebo.

Subject analysis set title	Valid for Safety
Subject analysis set type	Full analysis

Subject analysis set description:

84 of 85 subjects received study medication. The Valid for Safety set (VfS) comprised 84 subjects, of whom 57 received AM-101 and 27 Placebo.

Reporting group values	Valid for Efficacy	Valid for Safety	
Number of subjects	66	84	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	

Adolescents (12-17 years)	0	0	
Adults (18-64 years)	66	84	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	40.9	39.7	
standard deviation	± 11.93	± 12.18	
Gender categorical Units: Subjects			
Female	20	24	
Male	46	60	
Ethnic group Units: Subjects			
Caucasian	65	82	
African	0	0	
Asian	0	0	
Hispanic	1	2	

End points

End points reporting groups

Reporting group title	AM-101 0.81 mg/mL gel (single)
Reporting group description:	
Single intratympanic administration of AM-101 0.81 mg/mL gel at D0	
Reporting group title	Placebo (single)
Reporting group description:	
Single intratympanic administration of placebo gel at D0.	
Reporting group title	AM-101 0.81 mg/mL gel (triple)
Reporting group description:	
Triple intratympanic administration over 2 weeks of AM-101 0.81 mg/mL gel at D0, D7, D14	
Reporting group title	Placebo (triple)
Reporting group description:	
Triple intratympanic administration over 2 weeks of placebo gel at D0, D7, D14	
Subject analysis set title	Valid for Efficacy
Subject analysis set type	Per protocol
Subject analysis set description:	
Major protocol violators have been excluded. 66 subjects were included in the Valid for Efficacy set (VfE), of whom 44 received AM-101 and 22 Placebo.	
Subject analysis set title	Valid for Safety
Subject analysis set type	Full analysis
Subject analysis set description:	
84 of 85 subjects received study medication. The Valid for Safety set (VfS) comprised 84 subjects, of whom 57 received AM-101 and 27 Placebo.	

Primary: Efficacy: TLQ improvement from baseline to FUV3

End point title	Efficacy: TLQ improvement from baseline to FUV3
End point description:	
The primary efficacy outcome was the absolute improvement in tinnitus loudness (TLQ) by magnitude estimation from Baseline (TV1) to 90 days following the last injection (FUV3), i.e. TLQ(TV1)-TLQ(FUV3). Analysis was performed on valid for efficacy data set.	
End point type	Primary
End point timeframe:	
Baseline (TV1) up to end of study (FUV3)	

End point values	AM-101 0.81 mg/mL gel (single)	Placebo (single)	AM-101 0.81 mg/mL gel (triple)	Placebo (triple)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	10[1]	23	12[2]
Units: 0 - 100 numerical rating scale				
arithmetic mean (standard deviation)	21.4 (± 20.1)	11.3 (± 34.2)	12.9 (± 23.9)	1.9 (± 20.3)

Notes:

[1] - pooled placebo (n=22) data set used for analysis, subjects analyzed in single group (n=43)

[2] - pooled placebo (n=22) data set used for analysis, subjects analyzed in triple group (n=45)

Statistical analyses

Statistical analysis title	Improvement in tinnitus loudness from baseline
Comparison groups	AM-101 0.81 mg/mL gel (single) v Placebo (single) v AM-101 0.81 mg/mL gel (triple) v Placebo (triple)
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.084
Method	ANCOVA

Notes:

[3] - ANCOVA model for the trend in group means for pooled placebo, single-dose AM-101 and triple-dose AM-101

Primary: Safety: Incidence of change in hearing threshold ≥ 15 dB from Baseline (TV1) to FUV2

End point title	Safety: Incidence of change in hearing threshold ≥ 15 dB from Baseline (TV1) to FUV2

End point description:

Change in hearing threshold ≥ 15 dB from Baseline (TV1) to FUV2 at the average of two contiguous test frequencies in the treated ear.

No statistics computed for triple treatment comparison, because row or column sum is zero.

End point type	Primary

End point timeframe:

From baseline (TV1) to FUV2

End point values	AM-101 0.81 mg/mL gel (single)	Placebo (single)	AM-101 0.81 mg/mL gel (triple)	Placebo (triple)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	11	25	12
Units: number of subjects	1	0	0	0

Statistical analyses

Statistical analysis title	Single treatment

Statistical analysis description:

Statistical analysis if Placebo vs. AM-101 treatment was statistically significant different.

Comparison groups	AM-101 0.81 mg/mL gel (single) v Placebo (single)
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other
P-value	= 1
Method	Fisher exact

Secondary: PK: Maximum plasma drug concentration level (Cmax) - Esketamine

End point title	PK: Maximum plasma drug concentration level (Cmax) - Esketamine[4]

End point description:

The maximum plasma concentration (Cmax) for each subject was derived directly from their plasma concentration-time profiles.
In 11 of 11 subjects concentrations of Esketamine were found at or above the lower limit of quantitation (LLOQ) of 0.1 ng/mL. Therefore the samples of 11 patients
could be included in the pharmacokinetic (PK) analysis.

Statistics N/A - Standard PK analysis methods were used.

End point type	Secondary

End point timeframe:

Sampling at treatment visit (TV) 1 prior to and 15, 30, 45, 60, 180, and 360 minutes after treatment of the (first) ear.

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Of 18 subjects in single dose arms, 11 subjects received AM-101. The samples of the 11 AM-101 dosed subjects were used for PK analysis.

End point values	AM-101 0.81 mg/mL gel (single)			
Subject group type	Reporting group			
Number of subjects analysed	11[5]			
Units: ng/mL				
arithmetic mean (standard deviation)	0.2 (± 0.13)			

Notes:

[5] - See description in Cmax - Esketamine

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Time to maximum plasma concentration (Tmax) - Esketamine

End point title	PK: Time to maximum plasma concentration (Tmax) - Esketamine[6]

End point description:

The time to maximum plasma drug concentration was derived directly from the patient's plasma concentration-time profile.

End point type	Secondary

End point timeframe:

Sampling at treatment visit (TV) 1 prior to and 15, 30, 45, 60, 180, and 360 minutes after treatment of the (first) ear.

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Of 18 subjects in single dose arms, 11 subjects received AM-101. The samples of the 11 AM-101 dosed subjects were used for PK analysis.

End point values	AM-101 0.81 mg/mL gel (single)			
Subject group type	Reporting group			
Number of subjects analysed	11[7]			
Units: min				
number (not applicable)	55.9			

Notes:

[7] - See description in Cmax - Esketamine

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Area under the plasma concentration-time curve - Esketamine

End point title	PK: Area under the plasma concentration-time curve - Esketamine[8]

End point description:

End point type	Secondary

End point timeframe:

Sampling at treatment visit (TV) 1 prior to and 15, 30, 45, 60, 180, and 360 minutes after treatment of the (first) ear.

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Of 18 subjects in single dose arms, 11 subjects received AM-101. The samples of the 11 AM-101 dosed subjects were used for PK analysis.

End point values	AM-101 0.81 mg/mL gel (single)			
Subject group type	Reporting group			
Number of subjects analysed	11[9]			
Units: ng min/mL				
number (not applicable)	20.67			

Notes:

[9] - See description in Cmax - Esketamine

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Maximum plasma drug concentration level (Cmax) - S-Norketamine

End point title	PK: Maximum plasma drug concentration level (Cmax) - S-Norketamine[10]

End point description:

The maximum plasma concentration (Cmax) for each subject was derived directly from their plasma concentration-time profiles.
Concentrations of (S)-Norketamine could be quantified above the lower limit of quantification (LLOQ) of 0.1 ng/mL only in 9 of 11 subjects; Concentrations were all below 30 ng/mL.

Statistics N/A - Standard PK analysis methods were used.

End point type	Secondary

End point timeframe:

Sampling at treatment visit (TV) 1 prior to and 15, 30, 45, 60, 180, and 360 minutes after treatment of the (first) ear.

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Of 18 subjects in single dose arms, 11 subjects received AM-101. The samples of the 11 AM-101 dosed subjects were used for PK analysis.

End point values	AM-101 0.81 mg/mL gel (single)			
Subject group type	Reporting group			
Number of subjects analysed	11[11]			
Units: ng/mL				
arithmetic mean (standard deviation)	0.13 (± 0.09)			

Notes:

[11] - See description in Cmax - (S)-Norketamine

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Time to maximum plasma concentration (Tmax) - S-Norketamine

End point title	PK: Time to maximum plasma concentration (Tmax) - S-Norketamine[12]

End point description:

The time to maximum plasma drug concentration was derived directly from the patient's plasma concentration-time profile.

End point type	Secondary

End point timeframe:

Sampling at treatment visit (TV) 1 prior to and 15, 30, 45, 60, 180, and 360 minutes after treatment of the (first) ear.

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Of 18 subjects in single dose arms, 11 subjects received AM-101. The samples of the 11 AM-101 dosed subjects were used for PK analysis.

End point values	AM-101 0.81 mg/mL gel (single)			
Subject group type	Reporting group			
Number of subjects analysed	11[13]			
Units: min				
number (not applicable)	233.3			

Notes:

[13] - See description in Cmax - (S)-Norketamine

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Area under the plasma concentration-time curve - S-Norketamine

End point title	PK: Area under the plasma concentration-time curve - S-Norketamine[14]

End point description:

End point type	Secondary

End point timeframe:

Sampling at treatment visit (TV) 1 prior to and 15, 30, 45, 60, 180, and 360 minutes after treatment of the (first) ear.

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Of 18 subjects in single dose arms, 11 subjects received AM-101. The samples of the 11 AM-101 dosed subjects were used for PK analysis.

End point values	AM-101 0.81 mg/mL gel (single)			
Subject group type	Reporting group			
Number of subjects analysed	11[15]			
Units: ng min/mL				
number (not applicable)	30.67			

Notes:

[15] - See description in Cmax - (S)-Norketamine

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline to end of study at all visits.

Adverse event reporting additional description:

Assessed by investigator at all visits.

The occurrence of a treatment emergent adverse event in the same subject more than once was counted only once for non-serious adverse events.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Placebo (single)

Reporting group description:

Single administration of placebo gel at D0.

Reporting group title	AM-101 0.81 mg/mL gel (single)

Reporting group description:

Single administration of AM-101 0.81 mg/mL gel at D0

Reporting group title	Placebo (triple)

Reporting group description:

Triple administration over 2 weeks of placebo gel at D0, D7, D14

Reporting group title	AM-101 0.81 mg/mL gel (triple)

Reporting group description:

Triple administration over 2 weeks of AM-101 0.81 mg/mL gel at D0, D7, D14

Serious adverse events	Placebo (single)	AM-101 0.81 mg/mL gel (single)	Placebo (triple)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 14 (0.00%)	0 / 32 (0.00%)	0 / 13 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Cubital tunnel syndrome			
subjects affected / exposed	0 / 14 (0.00%)	0 / 32 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	AM-101 0.81 mg/mL gel (triple)		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 25 (4.00%)		
number of deaths (all causes)	0		

number of deaths resulting from adverse events	0		
Nervous system disorders			
Cubital tunnel syndrome			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2.4 %

Non-serious adverse events	Placebo (single)	AM-101 0.81 mg/mL gel (single)	Placebo (triple)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 14 (64.29%)	15 / 32 (46.88%)	8 / 13 (61.54%)
Investigations			
Blood triglycerides increased			
subjects affected / exposed	0 / 14 (0.00%)	1 / 32 (3.13%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 14 (7.14%)	0 / 32 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	0 / 14 (0.00%)	2 / 32 (6.25%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Ear pain			
subjects affected / exposed	1 / 14 (7.14%)	3 / 32 (9.38%)	1 / 13 (7.69%)
occurrences (all)	1	3	1
Hypoacusis			
subjects affected / exposed	1 / 14 (7.14%)	3 / 32 (9.38%)	3 / 13 (23.08%)
occurrences (all)	1	3	3
Tinnitus			
subjects affected / exposed	3 / 14 (21.43%)	4 / 32 (12.50%)	3 / 13 (23.08%)
occurrences (all)	3	4	3
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 14 (0.00%)	1 / 32 (3.13%)	1 / 13 (7.69%)
occurrences (all)	0	1	1

Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 32 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 32 (0.00%)	2 / 13 (15.38%)
occurrences (all)	0	0	2
Incision site haemorrhage	Additional description: *refers to verbatims "blood crust on location of paracentesis" / "tympanic membrane crusting on paracentesis site"		
subjects affected / exposed	2 / 14 (14.29%)	3 / 32 (9.38%)	0 / 13 (0.00%)
occurrences (all)	2	3	0
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	1 / 14 (7.14%)	1 / 32 (3.13%)	0 / 13 (0.00%)
occurrences (all)	1	1	0

Non-serious adverse events	AM-101 0.81 mg/mL gel (triple)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 25 (52.00%)		
Investigations			
Blood triglycerides increased			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Ear pain			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Hypoacusis			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		

Tinnitus			
subjects affected / exposed	4 / 25 (16.00%)		
occurrences (all)	4		
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Incision site haemorrhage	Additional description: *refers to verbatims "blood crust on location of paracentesis" / "tympanic membrane crusting on paracentesis site"		
subjects affected / exposed	5 / 25 (20.00%)		
occurrences (all)	5		
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 November 2011	- Change of primary efficacy variable from MML to TLQ to take into account results from study AM-101-CL-08-01 and preliminary results from study AM-101-CL-10-01. - Elimination of MML ≥ 5 dB (SL) as inclusion criterion to reflect relegation of MML from primary to secondary efficacy endpoint. Correspondingly, also exclusion criterion "Tinnitus that is not completely maskable" was removed. - Increase of sample size from 36 to 72 to reflect change in primary endpoint. - Addition of THI-12 questionnaire and 3 specific sleep impact questions as secondary efficacy outcome variables. - Exclusion of cases of ISSNHL-related tinnitus due to lack of clear efficacy in study AM-101-CL-08-01. Examinations specifically required for ISSNHL subjects, i.e. speech audiometry and auditory brainstem response, were removed. - Change in dose regimen for Cohort 2 from 3 doses over 3 consecutive days to 3 doses over 2 weeks to evaluate an additional / other dose regimen than applied in study AM-101-CL-08-01. The study duration for Cohort 2 was extended from 90 to 104 (= 90 + 14) days. - Addition of Belgium, Poland, and Germany as study countries with Auris Medical AG as Sponsor for European sites.
26 April 2012	- Removal of blood sampling for PK analysis in Cohort 2 as redundant based on reassessment of known PK data. - Phone contact with subjects added at Day 60 to better collect possible AEs between FUV2 and FUV3.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported