Clinical trial results:
Efficacy and Safety of AM-101 in the Treatment of Acute Peripheral Tinnitus 2 (TACTT2)

Summary

EudraCT number	2013-005587-26
Trial protocol	CZ
Global end of trial date	22 June 2016

Results information

Result version number	v2 (current)
This version publication date	01 March 2018
First version publication date	21 December 2017
Version creation reason	• Correction of full data set Total numbers of non-serious adverse events needs to be corrected to contain only the number subjects that was affected by AEs equal/above the 2% threshold. Phone number in field sponsor contact needs to be corrected.

Trial information

Trial identification

Sponsor protocol code	AM-101-CL-12-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01803646
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Auris Medical Inc.
Sponsor organisation address	500 North Michigan Avenue, Suite 600, Chicago, Illinois, United States, 60611
Public contact	Thomas Meyer, Auris Medical Inc, +1 312 396 4150, hear@aurismedical.com
Scientific contact	Thomas Meyer, Auris Medical Inc, +1 3123964150, hear@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	23 November 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 June 2016
Global end of trial reached?	Yes
Global end of trial date	22 June 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is the evaluation and confirmation of the efficacy of repeated i.t. AM-101 injections in the treatment of acute peripheral tinnitus

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 the ethical principles outlined in the Declaration of Helsinki dated 1989, or in their most current version.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 February 2014
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	Czech Republic: 64
Country: Number of subjects enrolled	Canada: 34
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	Korea, Republic of: 27
Country: Number of subjects enrolled	Turkey: 11
Country: Number of subjects enrolled	United States: 204
Worldwide total number of subjects	343
EEA total number of subjects	64

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)	313
From 65 to 84 years	30
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 86 sites were initiated in Canada, the United States, the Czech Republic, Israel, Turkey and Republic of South Korea. In total, 69 sites screened each at least 1 subject and 64 sites randomized subjects for treatment.

Pre-assignment

Screening details:

The study consisted of a screening period (Day [D] -14 to D0). 478 subjects had been assessed for eligibility, of which 135 have been excluded for the following reasons:
- not meeting inclusion criteria (n=98)
- declined to participate (n=30)
- other reasons (n=7)

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 0.87 mg/mL gel

Arm description:

Three intratympanic administration of AM-101 0.87 mg/mL gel within 5 days (D0-D4)

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:

Three intratympanic administrations of AM-101 0.87 mg/mL (0.25 mL). In case of eligible bilateral tinnitus subjects, both ears were treated.

Arm title	Placebo

Arm description:

Three intratympanic administration of placebo gel within 5 days (D0-D4).

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:

Three intratympanic administrations of AM-101 0 mg/mL (0.25 mL). In case of eligible bilateral tinnitus subjects, both ears were treated.

Number of subjects in period 1	AM-101 0.87 mg/mL gel	Placebo
Started	204	139
Completed	187	129
Not completed	17	10
Randomization error	1	2
Consent withdrawn by subject	9	6
Adverse event, non-fatal	1	1
Lost to follow-up	5	1
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	AM-101 0.87 mg/mL gel
Reporting group description:	
Three intratympanic administration of AM-101 0.87 mg/mL gel within 5 days (D0-D4)	
Reporting group title	Placebo
Reporting group description:	
Three intratympanic administration of placebo gel within 5 days (D0-D4).	

Reporting group values	AM-101 0.87 mg/mL gel	Placebo	Total
Number of subjects	204	139	343
Age categorical Units: Subjects			
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	188	125	313
From 65-84 years	16	14	30
Age continuous Units: years			
arithmetic mean	43.4	44.2	
standard deviation	± 14.6	± 15.2	-
Gender categorical Units: Subjects			
Female	43	37	80
Male	161	102	263

Subject analysis sets	
Subject analysis set title	Valid for Safety
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
This analysis set included all subjects who were treated with at least 1 intratympanic injection of either AM-101 or placebo. It was used as a general analysis set for safety and tolerability data. Comprises 336 subjects of 343 enrolled subjects.	
Subject analysis set title	Valid for Efficacy
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
This analysis set was defined based on the Intention to Treat principle. It was used as the primary set for efficacy evaluation. It includes all subjects who: • were treated with at least 1 intratympanic injection of either AM-101 or placebo • had a valid TLQ (NRSLoudest) rating at Baseline and at least 1 valid post-Baseline TLQ (NRSLoudest) rating or had a valid TFI rating at Baseline and at least 1 valid post-Baseline TFI rating.	

Reporting group values	Valid for Safety	Valid for Efficacy	
Number of subjects	336	326	
Age categorical Units: Subjects			
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	306	297	

From 65-84 years	30	29	

Age continuous Units: years arithmetic mean standard deviation	±	±	
Gender categorical Units: Subjects			
Female	78	78	
Male	258	248	

End points

End points reporting groups

Reporting group title	AM-101 0.87 mg/mL gel
Reporting group description:	
Three intratympanic administration of AM-101 0.87 mg/mL gel within 5 days (D0-D4)	
Reporting group title	Placebo
Reporting group description:	
Three intratympanic administration of placebo gel within 5 days (D0-D4).	
Subject analysis set title	Valid for Safety
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
This analysis set included all subjects who were treated with at least 1 intratympanic injection of either AM-101 or placebo. It was used as a general analysis set for safety and tolerability data. Comprises 336 subjects of 343 enrolled subjects.	
Subject analysis set title	Valid for Efficacy
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
This analysis set was defined based on the Intention to Treat principle. It was used as the primary set for efficacy evaluation. It includes all subjects who: • were treated with at least 1 intratympanic injection of either AM-101 or placebo • had a valid TLQ (NRSLoudest) rating at Baseline and at least 1 valid post-Baseline TLQ (NRSLoudest) rating or had a valid TFI rating at Baseline and at least 1 valid post-Baseline TFI rating.	

Primary: Efficacy: Patient-reported TLQ Improvement from Baseline to FUV3

End point title	Efficacy: Patient-reported TLQ Improvement from Baseline to FUV3
End point description:	
Improvement in patient-reported tinnitus loudness TLQ NRSLoudest from baseline to FUV3.	
End point type	Primary
End point timeframe:	
Baseline (TV1) up to end of study (FUV3)	

End point values	AM-101 0.87 mg/mL gel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	129		
Units: Numerical rating scale (0-10)				
least squares mean (confidence interval 95%)	0.80 (0.51 to 1.08)	0.63 (0.38 to 0.87)		

Statistical analyses

Statistical analysis title	Improvement in tinnitus loudness from baseline
Comparison groups	AM-101 0.87 mg/mL gel v Placebo

Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.32
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.51
upper limit	0.17

Primary: Co-Primary Efficacy: Improvement in TFI total score from baseline to FUV3	
End point title	Co-Primary Efficacy: Improvement in TFI total score from baseline to FUV3

End point description:

The final TFI is a patient reported outcome questionnaire and contains 25 questions. It includes eight subscales: Intrusive, Sense of Control, Cognitive, Sleep, Auditory, Relaxation, Quality of Life, and Emotional.
The TFI total score is considered as valid if there are evaluable answers for at least 19 of the 25 items (76% of items) (Meikle et al. 2012).

End point type	Primary

End point timeframe:

Improvement in TFI total score from baseline to FUV3

End point values	AM-101 0.87 mg/mL gel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	180	121		
Units: Total score of 25 questions				
least squares mean (confidence interval 95%)	10.4 (6.5 to 14.3)	9.6 (5.9 to 13.3)		

Statistical analyses

Statistical analysis title	Improvement TFI total score at FUV3
Comparison groups	AM-101 0.87 mg/mL gel v Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.63
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.79

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	2.4

Primary: Safety: Frequency of subjects with deterioration of hearing at FUV2	
End point title	Safety: Frequency of subjects with deterioration of hearing at FUV2

End point description:

Deterioration of hearing (Air and Bone conduction) in the treated ear at FUV2.
Deterioration is defined as a deterioration of hearing threshold of at least 15 dB from Baseline at the average of 2 contiguous frequencies.

End point type	Primary

End point timeframe:

From baseline to FUV2

End point values	AM-101 0.87 mg/mL gel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	130		
Units: number subjects				
Air conduction	12	9		
Bone conduction	3	4		

Statistical analyses

Statistical analysis title	Deterioration of hearing for air conduction
Comparison groups	AM-101 0.87 mg/mL gel v Placebo
Number of subjects included in analysis	323
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.821
Method	Fisher exact

Statistical analysis title	Deterioration of hearing for bone conduction
Comparison groups	AM-101 0.87 mg/mL gel v Placebo

Number of subjects included in analysis	323
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact

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.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	AM-101
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	AM-101	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 201 (2.49%)	1 / 135 (0.74%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Lower limb fracture			
subjects affected / exposed	1 / 201 (0.50%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	1 / 201 (0.50%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 201 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Generalised tonic-clonic seizure			

subjects affected / exposed	1 / 201 (0.50%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mental disorder			
subjects affected / exposed	1 / 201 (0.50%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 201 (0.50%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	AM-101	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	63 / 201 (31.34%)	38 / 135 (28.15%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	10 / 201 (4.98%)	1 / 135 (0.74%)	
occurrences (all)	10	1	
Headache			
subjects affected / exposed	11 / 201 (5.47%)	6 / 135 (4.44%)	
occurrences (all)	11	6	
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	5 / 201 (2.49%)	1 / 135 (0.74%)	
occurrences (all)	5	1	
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	14 / 201 (6.97%)	8 / 135 (5.93%)	
occurrences (all)	14	8	
Ear pain			

subjects affected / exposed	16 / 201 (7.96%)	10 / 135 (7.41%)	
occurrences (all)	16	10	
Hypoacusis			
subjects affected / exposed	8 / 201 (3.98%)	4 / 135 (2.96%)	
occurrences (all)	8	4	
Tinnitus			
subjects affected / exposed	8 / 201 (3.98%)	5 / 135 (3.70%)	
occurrences (all)	8	5	
Tympanic membrane perforation			
subjects affected / exposed	5 / 201 (2.49%)	4 / 135 (2.96%)	
occurrences (all)	5	4	
Vertigo			
subjects affected / exposed	2 / 201 (1.00%)	4 / 135 (2.96%)	
occurrences (all)	2	4	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	4 / 201 (1.99%)	2 / 135 (1.48%)	
occurrences (all)	4	2	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	7 / 201 (3.48%)	1 / 135 (0.74%)	
occurrences (all)	7	1	
Insomnia			
subjects affected / exposed	4 / 201 (1.99%)	0 / 135 (0.00%)	
occurrences (all)	4	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 201 (2.99%)	4 / 135 (2.96%)	
occurrences (all)	6	4	
Sinusitis			
subjects affected / exposed	4 / 201 (1.99%)	0 / 135 (0.00%)	
occurrences (all)	4	0	
Upper respiratory tract infection			
subjects affected / exposed	5 / 201 (2.49%)	2 / 135 (1.48%)	
occurrences (all)	5	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28608739