Clinical trial results:
AM-101 in the Post-Acute Treatment of Peripheral Tinnitus 1 (AMPACT1) – an open-label extension to the TACTT2 study

Summary

EudraCT number	2013-005588-24
Trial protocol	CZ
Global end of trial date	19 January 2017

Results information

Result version number	v1
This version publication date	25 February 2018
First version publication date	25 February 2018

Trial information

Trial identification

Sponsor protocol code	AM-101-CL-12-03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01934010
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., +1 312 396 4150, 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 May 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 January 2017
Global end of trial reached?	Yes
Global end of trial date	19 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the phase 3 open-label extension (OLE) study is the evaluation of the safety and local tolerance of up to 3 quarterly treatment cycles each with 3 repeated doses of AM-101 0.87 mg/mL in subjects previously treated in the scope of the TACTT2 study with either AM-101 0.87 mg/mL or placebo.
A total cumulative observational period of 1 year in subjects with acute persistent peripheral tinnitus who were previously enrolled into and completed TACTT2 was reached.
Subjects who completed TACTT2, could roll-over into treatment cycle 1 of this study (AMPACT1). After completion of treatment cycle 1 they were free to decide if they want to continue with treatment cycle 2. Same for treatment cycle 3.
In total 257 subjects were treated in AMPACT1 of which:
- 114 subjects participated only in the first cycle,
- 67 subjects participated in the first 2 treatment cycles,
- 76 subjects participated in all 3 treatment cycles.

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	02 June 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: 53
Country: Number of subjects enrolled	Canada: 24
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	Korea, Republic of: 16
Country: Number of subjects enrolled	Turkey: 5
Country: Number of subjects enrolled	United States: 156
Worldwide total number of subjects	257
EEA total number of subjects	53

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)	231
From 65 to 84 years	26
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 260 subjects were enrolled and 257 subjects were treated in overall 59 active sites in Canada (6), the United States (35), the Czech Republic (7), Israel (2), Turkey (3) and Republic of South Korea (6).
Subjects could only participate if they had been previously enrolled and completed the participation in the TACTT2 study.

Pre-assignment

Screening details:

Main Inclusion Criteria:
Attendance at final visit FUV3 of TACTT2 study, aged 18 to 75 years, documented persistent subjective peripheral tinnitus following traumatic cochlear injury or otitis media (OM) with onset no longer than 3 months prior to randomization into TACTT2.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This study was an open-label extension study subsequent to the previous blinded, placebo controlled, randomized TACTT2 study. This study was requested by the FDA as long-term safety follow-up of repeated AM-101 injection cycles over 1 year.

Arms

Are arms mutually exclusive?	Yes
Arm title	1 Cycle AM-101

Arm description:

Subjects participated in 1 treatment cycle and received one round of 3 repeated doses of AM-101 gel (0.87 mg/mL) 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:

Subjects who participated only in treatment cycle 1, received three intratympanic administrations of AM-101 0.87 mg/mL (0.25 mL). In case of eligible bilateral tinnitus, both ears were treated.

Arm title	2 Cycles AM-101

Arm description:

Subjects that participated in 2 treatment cycles of the AMPACT1 study, received 3 repeated doses of AM-101 gel (0.87 mg/mL) within 5 days (D0 - D4) in cycle 1 and after final follow-up (D84) of cycle 1, they rolled-over to treatment cycle 2 receiving once more 3 repeated doses of AM-101 gel (0.87 mg/mL) within 5 days (D84 - D88).

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:

Subjects who participated in 2 treatment cycles, received 1x three intratympanic administrations of AM-101 0.87 mg/mL (0.25 mL) within 5 days and a second time three intratympanic injections of AM-101 0.87 mg/mL within 5 days after FUV3 (D84) of treatment cycle 1.

In case of eligible bilateral tinnitus, both ears were treated.

Arm title	3 Cycles AM-101

Arm description:

Subjects that participated in all 3 treatment cycles of the AMPACT1 study, received 3 x 3 repeated doses of AM-101 gel (0.87 mg/mL) within 5 days. The subjects could only roll-over if they completed the final follow-up of the previous cycle and were still eligible.
In cycle 1 treatment was within D0 - D4. Cycle 2 treatment within D84 - D88. And treatment for cycle 3 within D168-D172. Final follow-up after 3 treatment cycles was FUV9 (D252).

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:

Subjects who participated in all three treatment cycles, received 3 times three intratympanic administrations of AM-101 0.87 mg/mL (0.25 mL).
Please refer to arm description for details.
In case of eligible bilateral tinnitus, both ears were treated.

Number of subjects in period 1	1 Cycle AM-101	2 Cycles AM-101	3 Cycles AM-101
Started	114	67	76
Completed	91	56	74
Not completed	23	11	2
Consent withdrawn by subject	15	6	2
Adverse event, non-fatal	1	1	-
Lost to follow-up	7	4	-

Baseline characteristics

Reporting groups	
Reporting group title	1 Cycle AM-101
Reporting group description:	
Subjects participated in 1 treatment cycle and received one round of 3 repeated doses of AM-101 gel (0.87 mg/mL) within 5 days (D0 - D4)	
Reporting group title	2 Cycles AM-101
Reporting group description:	
Subjects that participated in 2 treatment cycles of the AMPACT1 study, received 3 repeated doses of AM-101 gel (0.87 mg/mL) within 5 days (D0 - D4) in cycle 1 and after final follow-up (D84) of cycle 1, they rolled-over to treatment cycle 2 receiving once more 3 repeated doses of AM-101 gel (0.87 mg/mL) within 5 days (D84 - D88).	
Reporting group title	3 Cycles AM-101
Reporting group description:	
Subjects that participated in all 3 treatment cycles of the AMPACT1 study, received 3 x 3 repeated doses of AM-101 gel (0.87 mg/mL) within 5 days. The subjects could only roll-over if they completed the final follow-up of the previous cycle and were still eligible. In cycle 1 treatment was within D0 - D4. Cycle 2 treatment within D84 - D88. And treatment for cycle 3 within D168-D172. Final follow-up after 3 treatment cycles was FUV9 (D252).	

Reporting group values	1 Cycle AM-101	2 Cycles AM-101	3 Cycles AM-101
Number of subjects	114	67	76
Age categorical Units: Subjects			
Adults (18-64 years)	106	61	64
From 65-84 years	8	6	12
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	43.1	44.7	47.6
standard deviation	± 14.1	± 13.9	± 15.5
Gender categorical Units: Subjects			
Female	25	17	21
Male	89	50	55

Reporting group values	Total		
Number of subjects	257		
Age categorical Units: Subjects			
Adults (18-64 years)	231		
From 65-84 years	26		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	63		

Male	194		

End points

End points reporting groups

Reporting group title	1 Cycle AM-101
Reporting group description:	
Subjects participated in 1 treatment cycle and received one round of 3 repeated doses of AM-101 gel (0.87 mg/mL) within 5 days (D0 - D4)	
Reporting group title	2 Cycles AM-101
Reporting group description:	
Subjects that participated in 2 treatment cycles of the AMPACT1 study, received 3 repeated doses of AM-101 gel (0.87 mg/mL) within 5 days (D0 - D4) in cycle 1 and after final follow-up (D84) of cycle 1, they rolled-over to treatment cycle 2 receiving once more 3 repeated doses of AM-101 gel (0.87 mg/mL) within 5 days (D84 - D88).	
Reporting group title	3 Cycles AM-101
Reporting group description:	
Subjects that participated in all 3 treatment cycles of the AMPACT1 study, received 3 x 3 repeated doses of AM-101 gel (0.87 mg/mL) within 5 days. The subjects could only roll-over if they completed the final follow-up of the previous cycle and were still eligible. In cycle 1 treatment was within D0 - D4. Cycle 2 treatment within D84 - D88. And treatment for cycle 3 within D168-D172. Final follow-up after 3 treatment cycles was FUV9 (D252).	

Primary: Frequency of subjects with a deterioration of hearing threshold (air conduction)

End point title	Frequency of subjects with a deterioration of hearing threshold (air conduction)
End point description:	
Valid for Safety Analysis Set was used. Please note that subjects with hearing deterioration are counted per arm and not per treatment cycle. This means that in Arm 1 deteriorations are counted for subjects that participated solely in 1 Cycle.	
End point type	Primary
End point timeframe:	
Frequencies of subjects with deterioration of hearing threshold in the treated ear(s) between different numbers of treatment cycles: TV1 to FUV2 (Cycle 1), TV4 to FUV5 (Cycle 2), TV7 to FUV8 (Cycle 3).	

End point values	1 Cycle AM-101	2 Cycles AM-101	3 Cycles AM-101	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	103[1]	67[2]	74[3]	
Units: Number subjects affected	10	2	2	

Notes:

[1] - Subjects who participated only in 1 treatment cycle and are valid for safety analysis.

[2] - Subjects who received two treatment cycles and are valid for safety analysis.

[3] - Subjects who received 3 treatment cycles and are valid for safety analysis.

Statistical analyses

Statistical analysis title	1 Cycle vs. 2 Cycles

Statistical analysis description:

Fisher's exact test to assess if there is a difference in deterioration of hearing threshold between subjects that received 1 treatment cycle with AM-101 or others who received 2 treatment cycles.

Comparison groups	1 Cycle AM-101 v 2 Cycles AM-101
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.128
Method	Fisher exact

Statistical analysis title	1 Cycle vs. 3 Cycles

Statistical analysis description:

Fisher's exact test to assess if there is a difference in deterioration of hearing threshold between subjects that received 1 treatment cycle with AM-101 or others who received 3 treatment cycles.

Comparison groups	1 Cycle AM-101 v 3 Cycles AM-101
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.075
Method	Fisher exact

Statistical analysis title	2 Cycles vs. 3 Cycles

Statistical analysis description:

Fisher's exact test to assess if there is a difference in deterioration of hearing threshold between subjects that received 2 treatment cycles with AM-101 or others who received 3 treatment cycles.

Comparison groups	2 Cycles AM-101 v 3 Cycles AM-101
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact

Primary: Frequency of subjects with a deterioration of hearing threshold (bone conduction)

End point title	Frequency of subjects with a deterioration of hearing threshold (bone conduction)

End point description:

Valid for Safety Analysis Set was used.

End point type	Primary

End point timeframe:

Frequencies of subjects with deterioration of hearing threshold in the treated ear(s) between different numbers of treatment cycles: TV1 to FUV2 (Cycle 1), TV4 to FUV5 (Cycle 2), TV7 to FUV8 (Cycle 3).

End point values	1 Cycle AM-101	2 Cycles AM-101	3 Cycles AM-101	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	103[4]	67[5]	75[6]	
Units: Number subjects affected	8	2	2	

Notes:

[4] - Subjects who participated only in 1 treatment cycle and are valid for safety analysis.

[5] - Subjects who received two treatment cycles and are valid for safety analysis.

[6] - Subjects who received 3 treatment cycles and are valid for safety analysis.

Statistical analyses

Statistical analysis title	1 Cycle vs. 2 Cycles
Comparison groups	1 Cycle AM-101 v 2 Cycles AM-101
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3186
Method	Fisher exact

Statistical analysis title	1 Cycle vs. 3 Cycles
Comparison groups	1 Cycle AM-101 v 3 Cycles AM-101
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.195
Method	Fisher exact

Statistical analysis title	2 Cycles vs. 3 Cycles
Comparison groups	2 Cycles AM-101 v 3 Cycles AM-101
Number of subjects included in analysis	142
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.

In non-serious adverse events section, under occurrences (all), reported numbers are "subjects affected".

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	1 Cycle AM-101
Reporting group description: -	
Reporting group title	2 Cycles AM-101
Reporting group description: -	
Reporting group title	3 Cycles AM-101

Reporting group description: -

Serious adverse events	1 Cycle AM-101	2 Cycles AM-101	3 Cycles AM-101
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 114 (1.75%)	1 / 67 (1.49%)	1 / 76 (1.32%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Liver function test increased			
subjects affected / exposed	1 / 114 (0.88%)	0 / 67 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lip and/or oral cavity cancer			
subjects affected / exposed	1 / 114 (0.88%)	0 / 67 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Adnexa uteri cyst			

subjects affected / exposed	0 / 114 (0.00%)	1 / 67 (1.49%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adnexa uteri mass			
subjects affected / exposed	0 / 114 (0.00%)	1 / 67 (1.49%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteonecrosis			
subjects affected / exposed	0 / 114 (0.00%)	0 / 67 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	1 Cycle AM-101	2 Cycles AM-101	3 Cycles AM-101
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 114 (21.93%)	25 / 67 (37.31%)	37 / 76 (48.68%)
Surgical and medical procedures			
Artificial crown procedure			
subjects affected / exposed	0 / 114 (0.00%)	0 / 67 (0.00%)	2 / 76 (2.63%)
occurrences (all)	0	0	2
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 114 (4.39%)	7 / 67 (10.45%)	9 / 76 (11.84%)
occurrences (all)	5	7	9
Dizziness			
subjects affected / exposed	0 / 114 (0.00%)	1 / 67 (1.49%)	2 / 76 (2.63%)
occurrences (all)	0	1	2
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	3 / 114 (2.63%)	9 / 67 (13.43%)	7 / 76 (9.21%)
occurrences (all)	3	9	7
Ear pain			

subjects affected / exposed	10 / 114 (8.77%)	13 / 67 (19.40%)	8 / 76 (10.53%)
occurrences (all)	10	13	8
Hypoacusis			
subjects affected / exposed	5 / 114 (4.39%)	4 / 67 (5.97%)	4 / 76 (5.26%)
occurrences (all)	5	4	4
Otorrhoea			
subjects affected / exposed	1 / 114 (0.88%)	4 / 67 (5.97%)	3 / 76 (3.95%)
occurrences (all)	1	4	3
Tinnitus			
subjects affected / exposed	0 / 114 (0.00%)	2 / 67 (2.99%)	5 / 76 (6.58%)
occurrences (all)	0	2	5
Tympanic membrane perforation			
subjects affected / exposed	0 / 114 (0.00%)	0 / 67 (0.00%)	3 / 76 (3.95%)
occurrences (all)	0	0	3
Vertigo			
subjects affected / exposed	0 / 114 (0.00%)	2 / 67 (2.99%)	1 / 76 (1.32%)
occurrences (all)	0	2	1
Eustachian tube dysfunction			
subjects affected / exposed	1 / 114 (0.88%)	0 / 67 (0.00%)	2 / 76 (2.63%)
occurrences (all)	1	0	2
Hyperacusis			
subjects affected / exposed	0 / 114 (0.00%)	0 / 67 (0.00%)	2 / 76 (2.63%)
occurrences (all)	0	0	2
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 114 (0.88%)	1 / 67 (1.49%)	2 / 76 (2.63%)
occurrences (all)	1	1	2
Infections and infestations			
Influenza			
subjects affected / exposed	0 / 114 (0.00%)	2 / 67 (2.99%)	0 / 76 (0.00%)
occurrences (all)	0	2	0
Nasopharyngitis			
subjects affected / exposed	4 / 114 (3.51%)	2 / 67 (2.99%)	6 / 76 (7.89%)
occurrences (all)	4	2	6
Bronchitis			

subjects affected / exposed	0 / 114 (0.00%)	0 / 67 (0.00%)	2 / 76 (2.63%)
occurrences (all)	0	0	2
Sinusitis			
subjects affected / exposed	0 / 114 (0.00%)	0 / 67 (0.00%)	2 / 76 (2.63%)
occurrences (all)	0	0	2
Upper respiratory tract infection			
subjects affected / exposed	0 / 114 (0.00%)	1 / 67 (1.49%)	2 / 76 (2.63%)
occurrences (all)	0	1	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