Clinical trial results:
Safety of AM-101 in Patients with Acute Inner Ear Tinnitus from Noise Trauma: a Dose-Finding Phase I/II Study

Summary

EudraCT number	2006-002692-41
Trial protocol	DE
Global end of trial date	15 March 2008

Results information

Result version number	v1 (current)
This version publication date	06 August 2016
First version publication date	06 August 2016

Trial information

Trial identification

Sponsor protocol code	AM-101-AAT-PHA1

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Laboratoires Auris SAS
Sponsor organisation address	CEEI Cap Alpha/ Avenue de l'Europe/ Clapiers, Montpellier Cedex 09, France, 34940
Public contact	see below at Affiliate, see below at Affiliate, 0041 61 2011350, ear@aurismedical.com
Scientific contact	see below at Affiliate, see below at Affiliate, 0041 61 2011350, ear@aurismedical.com
Sponsor organisation name	Affiliate = 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	07 August 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 March 2008
Global end of trial reached?	Yes
Global end of trial date	15 March 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was the evaluation of the tolerability of the dose range expected to be needed for later clinical studies and to determine the nature of adverse reactions that could be expected.
The secondary objectives of the study were the preliminary evaluation of the potential therapeutic benefit of AM-101 in the treatment of inner ear tinnitus as well as the evaluation of systemic exposure following a single intratympanic injection of AM-101 (pharmacokinetics).

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

Background therapy:

N/A

Evidence for comparator:

N/A

Actual start date of recruitment	01 March 2007
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	Germany: 24
Worldwide total number of subjects	24
EEA total number of subjects	24

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)	24
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was designed as a double-blind, randomised, placebo-controlled, dose escalation, phase I/II study of a single intratympanic administration of AM-101 with a 2 month follow-up period.
The study consisted of 4 dose cohorts (30, 90, 270 or 810 µg/ml) with 2 placebo and 4 verum patients per cohort. It involved 4 study sites in Germany.

Pre-assignment

Screening details:

Main inclusion criteria were: Age 18 - 60 years; permanent, stable, single tinnitus induced by acute acoustic trauma or sudden deafness; tinnitus on-set occurred within the past 3 months.

All screened patients had been randomised.

Period 1

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

Blinding implementation details:

The investigators as well as the subjects were blinded regarding the dose administered during the whole study. In particular, the gel formulation was of the same appearance for all doses and the placebo and revealed no differences during or following injection, neither to the investigator, nor to the patient.

Arms

Are arms mutually exclusive?	No
Arm title	AM-101 30 µg/ml

Arm description:

Each patient received study treatment comprising a single intratympanic injection of 30 µg/ml of AM-101 followed by a 2 month treatment-free follow-up period.

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:

0.25 ml of Esketamine HCl gel at a concentration of 30 µg/ml were injected.

Arm title	AM-101 90 µg/ml

Arm description:

Each patient received study treatment comprising a single intratympanic injection of 90 µg/ml of AM-101 followed by a 2 month treatment-free follow-up period.

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:

0.25 ml of Esketamine HCl gel at a concentration of 90 µg/ml were injected.

Arm title	AM-101 270 µg/ml

Arm description:

Each patient received study treatment comprising a single intratympanic injection of 270 µg/ml of AM-101 followed by a 2 month treatment-free follow-up period.

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:

0.25 ml of Esketamine HCl gel at a concentration of 270 µg/ml were injected.

Arm title	AM-101 810 µg/ml

Arm description:

Each patient received study treatment comprising a single intratympanic injection of 810 µg/ml of AM-101 followed by a 2 month treatment-free follow-up period.

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:

0.25 ml of Esketamine HCl gel at a concentration of 810 µg/ml were injected.

Arm title	AM-101 pooled set

Arm description:

This is a pooled set of all 4 treatment cohorts receiving AM-101 which was used for the primary analysis.

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:

0.25 ml of Esketamine HCl gel at a concentration of either 30, 90, 270 or 810 µg/ml were injected.

Arm title	Placebo

Arm description:

Matching placebo was administered following the same way (see above) with 2 subjects receiving placebo per dose cohort.

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:

0.25 mL of Placebo (not containing Esketamine HCl) were injected.

Number of subjects in period 1	AM-101 30 µg/ml	AM-101 90 µg/ml	AM-101 270 µg/ml
Started	4	4	4
Completed	4	4	3
Not completed	0	0	1
Consent withdrawn by subject	-	-	1

Number of subjects in period 1	AM-101 810 µg/ml	AM-101 pooled set	Placebo
Started	4	16	8
Completed	4	15	8
Not completed	0	1	0
Consent withdrawn by subject	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	AM-101 30 µg/ml
Reporting group description:	
Each patient received study treatment comprising a single intratympanic injection of 30 µg/ml of AM-101 followed by a 2 month treatment-free follow-up period.	
Reporting group title	AM-101 90 µg/ml
Reporting group description:	
Each patient received study treatment comprising a single intratympanic injection of 90 µg/ml of AM-101 followed by a 2 month treatment-free follow-up period.	
Reporting group title	AM-101 270 µg/ml
Reporting group description:	
Each patient received study treatment comprising a single intratympanic injection of 270 µg/ml of AM-101 followed by a 2 month treatment-free follow-up period.	
Reporting group title	AM-101 810 µg/ml
Reporting group description:	
Each patient received study treatment comprising a single intratympanic injection of 810 µg/ml of AM-101 followed by a 2 month treatment-free follow-up period.	
Reporting group title	AM-101 pooled set
Reporting group description:	
This is a pooled set of all 4 treatment cohorts receiving AM-101 which was used for the primary analysis.	
Reporting group title	Placebo
Reporting group description:	
Matching placebo was administered following the same way (see above) with 2 subjects receiving placebo per dose cohort.	

Reporting group values	AM-101 30 µg/ml	AM-101 90 µg/ml	AM-101 270 µg/ml
Number of subjects	4	4	4
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)	4	4	4
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	20	25.8	26.5
standard deviation	± 1.4	± 5.5	± 8.8
Gender categorical			
Units: Subjects			
Female	0	0	1
Male	4	4	3

Reporting group values	AM-101 810 µg/ml	AM-101 pooled set	Placebo
Number of subjects	4	16	8
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)	4	16	8
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	28.5	25.2	33
standard deviation	± 11.1	± 7.6	± 17.3
Gender categorical			
Units: Subjects			
Female	1	2	1
Male	3	14	7

Reporting group values	Total		
Number of subjects	24		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	24		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	3		
Male	21		

End points

End points reporting groups

Reporting group title	AM-101 30 µg/ml
Reporting group description:	
Each patient received study treatment comprising a single intratympanic injection of 30 µg/ml of AM-101 followed by a 2 month treatment-free follow-up period.	
Reporting group title	AM-101 90 µg/ml
Reporting group description:	
Each patient received study treatment comprising a single intratympanic injection of 90 µg/ml of AM-101 followed by a 2 month treatment-free follow-up period.	
Reporting group title	AM-101 270 µg/ml
Reporting group description:	
Each patient received study treatment comprising a single intratympanic injection of 270 µg/ml of AM-101 followed by a 2 month treatment-free follow-up period.	
Reporting group title	AM-101 810 µg/ml
Reporting group description:	
Each patient received study treatment comprising a single intratympanic injection of 810 µg/ml of AM-101 followed by a 2 month treatment-free follow-up period.	
Reporting group title	AM-101 pooled set
Reporting group description:	
This is a pooled set of all 4 treatment cohorts receiving AM-101 which was used for the primary analysis.	
Reporting group title	Placebo
Reporting group description:	
Matching placebo was administered following the same way (see above) with 2 subjects receiving placebo per dose cohort.	

Primary: Safety: Incidence of hearing loss grade 2 at two contiguous test frequencies at day 30 compared to baseline by treatment

End point title	Safety: Incidence of hearing loss grade 2 at two contiguous test frequencies at day 30 compared to baseline by treatment[1]

End point description:

The primary variable for the safety assessment was the incidence of a hearing loss ≥ Grade 2 (i.e. a loss of ≥ 25 dB) in any two contiguous kHz levels in the treated ear. The primary endpoint was on D30. Any hearing loss induced by the treatment and/or the procedure was hypothesised to become permanent by this time.

As defined in the statistical analysis plan: The total number and percent of primary safety events has been summarised by treatment. No formal statistical tests have been used to compare group differences.

The ITT analysis set was used for the primary data analyses and is identical with the safety set in this study.

The key study results are presented in the pooled verum data sets as the the primary study outcome.

End point type	Primary

End point timeframe:

Baseline to D30

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was performed. Number of events was zero.

End point values	AM-101 30 µg/ml	AM-101 90 µg/ml	AM-101 270 µg/ml	AM-101 810 µg/ml
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	3	4
Units: number subjects	0	0	0	0

End point values	AM-101 pooled set	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	8		
Units: number subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Efficacy: Changes in tinnitus severity as measured by the TBF-12

End point title	Efficacy: Changes in tinnitus severity as measured by the TBF-12

End point description:

The primary variable for the efficacy assessment was the measure of tinnitus handicap with the TBF-12 score. The primary endpoint was the change in TBF-12 between D0 and D30.

End point type	Primary

End point timeframe:

Baseline to Day 30

End point values	AM-101 30 µg/ml	AM-101 90 µg/ml	AM-101 270 µg/ml	AM-101 810 µg/ml
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	3	4
Units: TBF-12 score				
arithmetic mean (standard deviation)	0.5 (± 3.32)	0.25 (± 5.3)	-1.67 (± 5.5)	0.5 (± 2.7)

End point values	AM-101 pooled set	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	8		
Units: TBF-12 score				
arithmetic mean (standard deviation)	0 (± 3.9)	-0.13 (± 3)		

Statistical analyses

Statistical analysis title	Change in TBF-12 score from Baseline to D30
Comparison groups	Placebo v AM-101 pooled set
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed models analysis
Parameter estimate	Estimate
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.48
upper limit	7.68

Secondary: Efficacy: Improvement of the score of the tinnitus loudness question (TLQ)

End point title	Efficacy: Improvement of the score of the tinnitus loudness question (TLQ)

End point description:

The tinnitus loudness was documented by the patients via a 10 point visual analogue scale (VAS).

End point type	Secondary

End point timeframe:

Day 0 - Day 30

End point values	AM-101 30 µg/ml	AM-101 90 µg/ml	AM-101 270 µg/ml	AM-101 810 µg/ml
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	3	4
Units: 10 point visual analogue scale				
arithmetic mean (standard deviation)	-1 (± 1.15)	-1.5 (± 0.58)	-1.33 (± 0.58)	-0.5 (± 1)

End point values	AM-101 pooled set	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	8		
Units: 10 point visual analogue scale				

arithmetic mean (standard deviation)	-1.07 (± 0.88)	-0.31 (± 1.79)		

Statistical analyses

Statistical analysis title	Difference Placebo vs. AM-101 overall
Statistical analysis description: D0 to D30	
Comparison groups	Placebo v AM-101 pooled set
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed models analysis
Parameter estimate	Estimate
Point estimate	-0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.92
upper limit	1.8

Secondary: Efficacy: Change in minimum masking level (MML)

End point title	Efficacy: Change in minimum masking level (MML)

End point description:

A further secondary efficacy endpoint was the change from baseline to D30 in the minimum tinnitus masking level (MML) measured by the investigators. The binaural MML was assessed with a narrow band of noise.

End point type	Secondary
End point timeframe: Day 0 - Day 30	

End point values	AM-101 30 µg/ml	AM-101 90 µg/ml	AM-101 270 µg/ml	AM-101 810 µg/ml
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	3	4
Units: dB				
arithmetic mean (standard deviation)	-1 (± 6.48)	-2 (± 4)	1 (± 3.61)	-6.25 (± 2.5)

End point values	AM-101 pooled set	Placebo		

Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	8		
Units: dB				
arithmetic mean (standard deviation)	-2.29 (± 4.84)	-0.5 (± 1.87)		

Statistical analyses

Statistical analysis title	Difference Placebo vs. AM-101 overall
Statistical analysis description:	
D0 - D30	
Comparison groups	AM-101 pooled set v Placebo
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed models analysis
Parameter estimate	Estimate
Point estimate	1.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.77
upper limit	9.26

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

End point title	PK: Maximum plasma drug concentration level (Cmax) - Esketamine[2]

End point description:

Plasma samples of the 2 highest dose cohorts (270 and 810 µg/ml) were analysed for PK. Concentrations above lower limit of quantification (LLOQ) could be detected in only 1 of the 4 patients in the 270 g/ml dose group, but in 4 out of 4 in the 810 g/ml group. Therefore the samples of 5 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 on the day of treatment D0, with samples being drawn prior to treatment administration and 15 min, 30 min, 45 min, 1 hour, 3 hours and 6 hours after treatment.

Notes:

[2] - 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: For the PK analysis only patients from the 2 high dose cohorts were included.

End point values	AM-101 pooled set			
Subject group type	Reporting group			
Number of subjects analysed	5[3]			
Units: ng/mL				
arithmetic mean (standard deviation)	0.23 (± 0.06)			

Notes:

[3] - 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[4]

End point description:

End point type	Secondary

End point timeframe:

see Cmax - Esketamine

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: For the PK analysis only patients from the 2 high dose cohorts were included.

End point values	AM-101 pooled set			
Subject group type	Reporting group			
Number of subjects analysed	5[5]			
Units: hours				
arithmetic mean (standard deviation)	0.56 (± 0.31)			

Notes:

[5] - See description in Cmax - Esketamine

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Area under the plasma concentration-time curve (AUC 0-6) - Esketamine

End point title	PK: Area under the plasma concentration-time curve (AUC 0-6) - Esketamine[6]

End point description:

End point type	Secondary

End point timeframe:

see Cmax

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: For the PK analysis only patients from the 2 high dose cohorts were included.

End point values	AM-101 pooled set			
Subject group type	Reporting group			
Number of subjects analysed	5[7]			
Units: ng*h/mL				
arithmetic mean (standard deviation)	0.66 (± 0.12)			

Notes:

[7] - 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[8]

End point description:

see Cmax - Esketamine

End point type	Secondary

End point timeframe:

Sampling on the day of treatment D0, with samples being drawn prior to treatment administration and 15 min, 30 min, 45 min, 1 hour, 3 hours and 6 hours after treatment.

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: For the PK analysis only patients from the 2 high dose cohorts were included.

End point values	AM-101 pooled set			
Subject group type	Reporting group			
Number of subjects analysed	5[9]			
Units: ng/mL				
arithmetic mean (standard deviation)	0.15 (± 0.02)			

Notes:

[9] - See description in Cmax - Esketamine

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[10]

End point description:

End point type	Secondary

End point timeframe:

see Cmax - Esketamine

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: For the PK analysis only patients from the 2 high dose cohorts were included.

End point values	AM-101 pooled set			
Subject group type	Reporting group			
Number of subjects analysed	5[11]			
Units: hours				
arithmetic mean (standard deviation)	2.5 (± 1)			

Notes:

[11] - See description in Cmax - Esketamine

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Area under the plasma concentration-time curve (AUC 0-6) - S-Norketamine

End point title	PK: Area under the plasma concentration-time curve (AUC 0-6) - S-Norketamine[12]

End point description:

End point type	Secondary

End point timeframe:

see Cmax - Esketamine

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: For the PK analysis only patients from the 2 high dose cohorts were included.

End point values	AM-101 pooled set			
Subject group type	Reporting group			
Number of subjects analysed	5[13]			
Units: ng*h/mL				
arithmetic mean (standard deviation)	0.73 (± 0.16)			

Notes:

[13] - See description in Cmax - Esketamine

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

After single-dose treatment, study subjects were followed for 60 days with 3 follow-up visits at D7, D30 and D60. At each visit, AEs were recorded.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	9.1

Reporting groups

Reporting group title	AM-101 30 µg/ml
Reporting group description: -	
Reporting group title	AM-101 90 µg/ml
Reporting group description: -	
Reporting group title	AM-101 270 µg/ml
Reporting group description: -	
Reporting group title	AM-101 810 µg/ml
Reporting group description: -	
Reporting group title	AM-101 pooled set
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	AM-101 30 µg/ml	AM-101 90 µg/ml	AM-101 270 µg/ml
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	AM-101 810 µg/ml	AM-101 pooled set	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 8 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	AM-101 30 µg/ml	AM-101 90 µg/ml	AM-101 270 µg/ml
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 4 (50.00%)	2 / 4 (50.00%)	4 / 4 (100.00%)
Investigations			
Paracentesis ear abnormal			
subjects affected / exposed	0 / 4 (0.00%)	2 / 4 (50.00%)	1 / 4 (25.00%)
occurrences (all)	0	2	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	2 / 4 (50.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Neuromuscular blockade			
subjects affected / exposed	2 / 4 (50.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Paresthesia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Deafness unilateral			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Ear pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Middle ear inflammation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Tinnitus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Vertigo			

subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1

Non-serious adverse events	AM-101 810 µg/ml	AM-101 pooled set	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 4 (75.00%)	11 / 16 (68.75%)	6 / 8 (75.00%)
Investigations			
Paracentesis ear abnormal			
subjects affected / exposed	0 / 4 (0.00%)	3 / 16 (18.75%)	0 / 8 (0.00%)
occurrences (all)	0	3	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	2
Headache			
subjects affected / exposed	0 / 4 (0.00%)	2 / 16 (12.50%)	1 / 8 (12.50%)
occurrences (all)	0	2	1
Neuromuscular blockade			
subjects affected / exposed	0 / 4 (0.00%)	2 / 16 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Paresthesia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Deafness			

subjects affected / exposed	1 / 4 (25.00%)	1 / 16 (6.25%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Deafness unilateral			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Ear pain			
subjects affected / exposed	1 / 4 (25.00%)	1 / 16 (6.25%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Middle ear inflammation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Tinnitus			
subjects affected / exposed	1 / 4 (25.00%)	1 / 16 (6.25%)	1 / 8 (12.50%)
occurrences (all)	2	2	1
Vertigo			
subjects affected / exposed	1 / 4 (25.00%)	1 / 16 (6.25%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 4 (50.00%)	4 / 16 (25.00%)	1 / 8 (12.50%)
occurrences (all)	2	4	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	1 / 8 (12.50%)
occurrences (all)	0	1	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 May 2007	The aim of this amendment was to include an evaluation of the potential systemic exposure following a single intratympanic injection of AM-101. The pharmacokinetic characteristics of Esketamine in plasma were to be characterised at the two higher doses tested (270 µg/mL and 810 µg/mL), including determination of the parent and the principal metabolite (S)-Norketamine.
07 June 2007	- Patients with severe or disabling permanent inner ear tinnitus which set in with sudden deafness were included.
17 September 2007	- An interim analysis at the end of the 270 µg/mL dose cohort (after Day 7 of the last patient included in this cohort) was added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported