



Clinical trial results:

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

Summary

EudraCT number	2008-005178-10
Trial protocol	DE BE NL
Global end of trial date	10 May 2011

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-CL-08-01
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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	11 January 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 May 2011
Global end of trial reached?	Yes
Global end of trial date	10 May 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial was the evaluation of the therapeutic benefit of 3 repeated dose intratympanic AM-101 injections in comparison to placebo in the treatment of acute inner ear tinnitus (onset within 3 months) following acute acoustic trauma (AAT), sudden deafness (idiopathic sudden sensorineural hearing loss, ISSNHL) or acute otitis media (OM).

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:

N/A

Evidence for comparator:

N/A

Actual start date of recruitment	31 March 2009
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: 123
Country: Number of subjects enrolled	Belgium: 66
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Poland: 56
Worldwide total number of subjects	248
EEA total number of subjects	248

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)	1
Adults (18-64 years)	247
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Twenty-eight European sites (academic tertiary referral centers and private ENT practices) participated in the study. A total of 284 patients were screened. Of these, 248 were randomised.

Pre-assignment

Screening details:

Main inclusion criteria were: Persistent tinnitus following AAT, sudden deafness or acute OM, with onset less than 3 months ago (ie, acute tinnitus); medical report of tinnitus provoking incident; age from 18 - 65 years.

Screening assessments were performed on Day 0.

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, Monitor, Data analyst, Investigator

Blinding implementation details:

The Sponsor, Investigators as well as the subjects were blinded regarding the treatment administered during the study. In particular, the gel formulation was of the same appearance for AM-101 and Placebo. The gel (either AM-101 or Placebo) revealed no differences during or following injection, neither to the Investigator, nor to the subject. The packaging was identical for all AM-101 doses and placebo. Subjects were randomized to one of the three treatment arms (low dose, high dose or placebo).

Arms

Are arms mutually exclusive?	Yes
Arm title	AM-101 low dose

Arm description:

Study drug (gel formulation) was administered on Days 0, 1, and 2 by intratympanic injection under local anesthesia of the tympanic membrane.

Patients came back for 3 further follow-up visits on Days 7, 30, and 90.

The study drug was provided in glass vials containing 0.7 mL of the gel formulation. One vial per patient per treatment visit was used to extract 0.25 mL for the intratympanic application.

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 0.27 mg/mL were injected. Only worse affected ear treated in case of bilateral tinnitus.

Arm title	AM-101 high dose
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Arm description:

see above at AM-101 low dose

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 0.81 mg/mL were injected. Only worse affected ear treated in case of bilateral tinnitus.

Arm title	Placebo
Arm description: see above at AM-101 low dose	
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. Only worse affected ear treated in case of bilateral tinnitus.

Number of subjects in period 1	AM-101 low dose	AM-101 high dose	Placebo
Started	78	84	86
Completed	74	75	83
Not completed	4	9	3
Consent withdrawn by subject	1	4	1
Significant medical condition	-	-	1
Other	-	1	-
Lost to follow-up	3	4	1

Baseline characteristics

Reporting groups

Reporting group title	AM-101 low dose
Reporting group description:	
Study drug (gel formulation) was administered on Days 0, 1, and 2 by intratympanic injection under local anesthesia of the tympanic membrane.	
Patients came back for 3 further follow-up visits on Days 7, 30, and 90.	
The study drug was provided in glass vials containing 0.7 mL of the gel formulation. One vial per patient per treatment visit was used to extract 0.25 mL for the intratympanic application.	
Reporting group title	AM-101 high dose
Reporting group description:	
see above at AM-101 low dose	
Reporting group title	Placebo
Reporting group description:	
see above at AM-101 low dose	

Reporting group values	AM-101 low dose	AM-101 high dose	Placebo
Number of subjects	78	84	86
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	1	0
Adults (18-64 years)	78	83	86
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	39	38.2	39.4
standard deviation	± 12.5	± 11.3	± 12.2
Gender categorical			
Units: Subjects			
Female	21	23	31
Male	57	61	55

Reporting group values	Total		
Number of subjects	248		
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)	1		
Adults (18-64 years)	247		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	75		
Male	173		

End points

End points reporting groups

Reporting group title	AM-101 low dose
Reporting group description: Study drug (gel formulation) was administered on Days 0, 1, and 2 by intratympanic injection under local anesthesia of the tympanic membrane. Patients came back for 3 further follow-up visits on Days 7, 30, and 90. The study drug was provided in glass vials containing 0.7 mL of the gel formulation. One vial per patient per treatment visit was used to extract 0.25 mL for the intratympanic application.	
Reporting group title	AM-101 high dose
Reporting group description: see above at AM-101 low dose	
Reporting group title	Placebo
Reporting group description: see above at AM-101 low dose	

Primary: Efficacy: Differences between treatment groups in the change of MML from baseline to Day 90

End point title	Efficacy: Differences between treatment groups in the change of MML from baseline to Day 90
End point description: The Minimum Masking Level was determined with a pulsed standard speech audiometry broadband masking noise and using the descending method of limits with bracketing at 5 dB resolution.	
Analysis performed on valid for efficacy analysis set.	
End point type	Primary
End point timeframe: Baseline to Day 90	

End point values	AM-101 low dose	AM-101 high dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	64	76	
Units: dB				
arithmetic mean (standard deviation)	7.76 (± 11.4)	7.65 (± 14.3)	9.19 (± 15.1)	

Statistical analyses

Statistical analysis title	Global comparison
Statistical analysis description: For continuous efficacy end points, analysis of covariance (ANCOVA) models were used including treatment group as fixed class effect, and the baseline values (Day 0) of the respective end point as covariate.	
Comparison groups	AM-101 low dose v AM-101 high dose v Placebo

Number of subjects included in analysis	212
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9919
Method	ANCOVA

Primary: Efficacy - Co-Primary: Improvement of the score of the tinnitus loudness question (TLQ)

End point title	Efficacy - Co-Primary: Improvement of the score of the tinnitus loudness question (TLQ)
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End point description:

For determining tinnitus loudness, subjects were presented the question: "Describe the loudness of your tinnitus right now using a scale from 0-100". The scale was anchored at the extremes 0 = no tinnitus heard, respectively not annoying at all, and 100 = very loud, respectively very annoying.

TLQ at Day 90 was defined as co-primary endpoint. Analysis performed on valid for efficacy data set.

End point type	Primary
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End point timeframe:

Day 0 to Day 90.

End point values	AM-101 low dose	AM-101 high dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	71	64	75	
Units: 0 - 100 numerical rating scale				
arithmetic mean (standard deviation)	16.1 (± 21.6)	22.2 (± 28.6)	15.9 (± 21.6)	

Statistical analyses

Statistical analysis title	Delta TLQ - Placebo vs AM-101 high dose
Comparison groups	Placebo v AM-101 high dose
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.089
Method	ANCOVA

Statistical analysis title	Delta TLQ - Placebo vs AM-101 low dose
Comparison groups	Placebo v AM-101 low dose

Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.59
Method	ANCOVA

Primary: Efficacy - Co-Primary: Improvement of the score of the tinnitus annoyance question (TAQ)

End point title	Efficacy - Co-Primary: Improvement of the score of the tinnitus annoyance question (TAQ)
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End point description:

For determining tinnitus annoyance, patients was presented the question: "Describe the annoyance of your tinnitus today using a scale from 0-100". The scale was anchored at the extremes 0 = no tinnitus heard, respectively not annoying at all, and 100 = very loud, respectively very annoying.

TLQ at Day 90 was defined as co-primary endpoint. Analysis performed on valid for efficacy data set.

End point type	Primary
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End point timeframe:

Day 0 to Day 90

End point values	AM-101 low dose	AM-101 high dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	71	64	75	
Units: 0 - 100 numerical rating scale				
arithmetic mean (standard deviation)	17.2 (± 20.7)	22.3 (± 28.9)	19.4 (± 21.8)	

Statistical analyses

Statistical analysis title	Delta TAQ - Placebo vs AM-101 low dose
Comparison groups	Placebo v AM-101 low dose
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.94
Method	ANCOVA

Statistical analysis title	Delta TAQ - Placebo vs AM-101 high dose
Comparison groups	AM-101 high dose v Placebo

Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.53
Method	ANCOVA

Primary: Safety: Incidence of change in hearing threshold \geq 15 dB from Baseline

End point title	Safety: Incidence of change in hearing threshold \geq 15 dB from Baseline
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End point description:

The primary safety endpoint was the number and percent of study subjects with a (clinically relevant) change in hearing threshold \geq 15 dB from Day 0 to Day 30 in any 2 contiguous test frequencies in the treated ear (only deteriorations were considered).

The frequency of patients meeting the primary safety end point was compared by treatment group with the Fisher exact test.

For analysis valid for safety analysis set was used (n = 248).

End point type	Primary
End point timeframe:	
Day 0 to Day 30.	

End point values	AM-101 low dose	AM-101 high dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	74	74	86	
Units: number subjects	4	3	2	

Statistical analyses

Statistical analysis title	Difference Placebo - AM-101 low dose
Comparison groups	Placebo v AM-101 low dose
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.42
Method	Fisher exact

Statistical analysis title	Difference Placebo - AM-101 high dose
Comparison groups	AM-101 high dose v Placebo

Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.66
Method	Fisher exact

Post-hoc: Efficacy: Improvement of the score of the tinnitus loudness question (TLQ) from baseline to Day 90 (subset AAT and OM)

End point title	Efficacy: Improvement of the score of the tinnitus loudness question (TLQ) from baseline to Day 90 (subset AAT and OM)
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End point description:

This was a post-hoc secondary analysis of the efficacy measures.

The subgroup comprises all subjects with acute acoustic trauma (AAT) and otitis media (OM) as tinnitus onset factors. In this subgroup with known tinnitus etiology related to cochlear glutamate excitotoxicity, the ANCOVA demonstrated superiority of the high dose with respect to placebo for the change in TLQ.

End point type	Post-hoc
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End point timeframe:

Day 0 to Day 90.

End point values	AM-101 low dose	AM-101 high dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	34	34	
Units: 0 – 100 numerical rating scale				
arithmetic mean (standard deviation)	13.4 (± 20.4)	24.4 (± 30.02)	9.7 (± 18.5)	

Statistical analyses

Statistical analysis title	Delta TLQ - Placebo vs AM-101 low dose
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Statistical analysis description:

Analysis was performed on valid for efficacy data set.

Comparison groups	Placebo v AM-101 low dose
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0926
Method	ANCOVA

Statistical analysis title	Delta TLQ - Placebo vs AM-101 high dose
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Statistical analysis description:

Analysis was performed on valid for efficacy data set.

Comparison groups	AM-101 high dose v Placebo
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Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0033
Method	ANCOVA

Post-hoc: Efficacy: Improvement of the score of the sleep impact questions from baseline to Day 90 (subset AAT and OM)

End point title	Efficacy: Improvement of the score of the sleep impact questions from baseline to Day 90 (subset AAT and OM)
End point description:	The subgroup comprises all subjects with acute acoustic trauma (AAT) and otitis media (OM) as Tinnitus onset factors. In this subgroup with known tinnitus etiology related to cochlear glutamate excitotoxicity, the ANCOVA demonstrated superiority of both dose groups with respect to placebo for the change in Sleep impact.
End point type	Post-hoc
End point timeframe:	D0 to D90.

End point values	AM-101 low dose	AM-101 high dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27	30	32	
Units: 0 – 100 numerical rating scale				
arithmetic mean (standard deviation)	0.4 (± 2.27)	0.69 (± 3.3)	-0.58 (± 2.4)	

Statistical analyses

Statistical analysis title	Delta Sleep Impact - Placebo vs AM-101 low dose
Statistical analysis description:	Analysis was performed on valid for efficacy data set.
Comparison groups	AM-101 low dose v Placebo
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.037
Method	ANCOVA

Statistical analysis title	Delta Sleep Impact - Placebo vs AM-101 high dose
Statistical analysis description:	Analysis was performed on valid for efficacy data set.
Comparison groups	Placebo v AM-101 high dose

Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	ANCOVA

Adverse events

Adverse events information

Timeframe for reporting adverse events:

At all Treatment Visits and Follow-Up 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 in non-serious adverse events.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	14.0
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Reporting groups

Reporting group title	AM-101 low dose
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Reporting group description: -

Reporting group title	AM-101 high dose
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

Serious adverse events	AM-101 low dose	AM-101 high dose	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 78 (2.56%)	1 / 84 (1.19%)	4 / 86 (4.65%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastric neoplasm			
subjects affected / exposed	0 / 78 (0.00%)	0 / 84 (0.00%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	1 / 78 (1.28%)	0 / 84 (0.00%)	0 / 86 (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
Blood and lymphatic system disorders			
Cardiomyopathy			

subjects affected / exposed	0 / 78 (0.00%)	0 / 84 (0.00%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Thrombocytopenia			
subjects affected / exposed	0 / 78 (0.00%)	0 / 84 (0.00%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Drug intolerance	Additional description: Drug intolerance to Propafenone		
subjects affected / exposed	1 / 78 (1.28%)	0 / 84 (0.00%)	0 / 86 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 78 (0.00%)	0 / 84 (0.00%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tinnitus			
subjects affected / exposed	1 / 78 (1.28%)	0 / 84 (0.00%)	0 / 86 (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
Hypoacusis			
subjects affected / exposed	1 / 78 (1.28%)	0 / 84 (0.00%)	0 / 86 (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
Psychiatric disorders			
Somatoform Disorder			
subjects affected / exposed	0 / 78 (0.00%)	0 / 84 (0.00%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental disorder			
subjects affected / exposed	0 / 78 (0.00%)	1 / 84 (1.19%)	0 / 86 (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

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

Non-serious adverse events	AM-101 low dose	AM-101 high dose	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 78 (44.87%)	42 / 84 (50.00%)	44 / 86 (51.16%)
Investigations			
Acoustic Stimulation Tests Abnormal			
subjects affected / exposed	3 / 78 (3.85%)	7 / 84 (8.33%)	9 / 86 (10.47%)
occurrences (all)	3	7	9
Audiogram Abnormal			
subjects affected / exposed	0 / 78 (0.00%)	2 / 84 (2.38%)	2 / 86 (2.33%)
occurrences (all)	0	2	2
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 78 (0.00%)	0 / 84 (0.00%)	2 / 86 (2.33%)
occurrences (all)	0	0	2
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 78 (0.00%)	1 / 84 (1.19%)	2 / 86 (2.33%)
occurrences (all)	0	1	2
Headache			
subjects affected / exposed	0 / 78 (0.00%)	4 / 84 (4.76%)	1 / 86 (1.16%)
occurrences (all)	0	4	1
General disorders and administration site conditions			
Injection Site Pain	Additional description: All events of injection site pain (and injection site warmth; n = 1) were reported from a single site.		
subjects affected / exposed	1 / 78 (1.28%)	2 / 84 (2.38%)	2 / 86 (2.33%)
occurrences (all)	1	2	2
Ear and labyrinth disorders			
Ear Discomfort			
subjects affected / exposed	1 / 78 (1.28%)	0 / 84 (0.00%)	3 / 86 (3.49%)
occurrences (all)	1	0	3
Ear Pain			

subjects affected / exposed occurrences (all)	3 / 78 (3.85%) 3	3 / 84 (3.57%) 3	1 / 86 (1.16%) 1
Hypoacusis subjects affected / exposed occurrences (all)	5 / 78 (6.41%) 5	1 / 84 (1.19%) 1	1 / 86 (1.16%) 1
Tinnitus subjects affected / exposed occurrences (all)	14 / 78 (17.95%) 14	15 / 84 (17.86%) 15	13 / 86 (15.12%) 13
Tympanic membrane hyperaemia subjects affected / exposed occurrences (all)	2 / 78 (2.56%) 2	2 / 84 (2.38%) 2	1 / 86 (1.16%) 1
Tympanic Membrane Perforation/Impaired Healing/Post procedural haemorrhage	Additional description: Tympanic membrane perforation, impaired healing (General Disorders and Administration Site Conditions) and post-procedural haemorrhage (Injury, Poisoning and Procedural Complications) have been pooled together.		
subjects affected / exposed occurrences (all)	10 / 78 (12.82%) 10	8 / 84 (9.52%) 8	9 / 86 (10.47%) 9
Vertigo subjects affected / exposed occurrences (all)	1 / 78 (1.28%) 1	0 / 84 (0.00%) 0	5 / 86 (5.81%) 5
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	0 / 78 (0.00%) 0	0 / 84 (0.00%) 0	2 / 86 (2.33%) 2
Sleep Disorders subjects affected / exposed occurrences (all)	0 / 78 (0.00%) 0	0 / 84 (0.00%) 0	2 / 86 (2.33%) 2
Infections and infestations Laryngitis subjects affected / exposed occurrences (all)	0 / 78 (0.00%) 0	0 / 84 (0.00%) 0	2 / 86 (2.33%) 2
Myringitis subjects affected / exposed occurrences (all)	1 / 78 (1.28%) 1	2 / 84 (2.38%) 2	1 / 86 (1.16%) 1
Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 78 (1.28%) 1	2 / 84 (2.38%) 2	1 / 86 (1.16%) 1
Upper Respiratory Tract Infection			

subjects affected / exposed	1 / 78 (1.28%)	0 / 84 (0.00%)	2 / 86 (2.33%)
occurrences (all)	1	0	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 February 2009	<ul style="list-style-type: none">- Inclusion criteria amended to include the definition of ISSNHL, clarification of range of inner ear hearing loss required at onset, and the necessity for subjects to be able to read and understand the relevant study documents.- Baseline assessments amended to include the addition of, and criteria for, Frenzel goggle examination, non-caloric nystagmography; and caloric nystagmography.- Tympanometry assessment added at Day 30.- Addition of secondary safety analyses.
15 May 2009	<ul style="list-style-type: none">- Inclusion criteria, objectives and subgroup analyses expanded to include subjects suffering from acute inner ear tinnitus following acute otitis media (OM) with acute inner ear hearing loss.- Exclusion criterion added to prohibit subjects taking any drug-based therapy for OM that was ongoing or was performed in the past 2 weeks.
28 August 2009	<ul style="list-style-type: none">- Inclusion criteria updated to remove the necessity for a confirmatory audiogram of hearing loss at the time of diagnosis.
03 May 2010	<ul style="list-style-type: none">- Clarification that routine measurements (eg, pure tone audiometry, otoscopy) to be done within 48 hours before obtaining informed consent and enrolment of the subject may be used as baseline assessment for the study. Modified procedures for study drug destruction.- Main body updated to include bone conducted measurements on Days 7 and 30.- Addition of baseline Minimum Masking Level value as a covariate in the statistical Analysis (analysis of covariance rather than analysis of variance) following updated Committee for Proprietary Medicinal Products (EMA) guidance.
21 April 2011	<ul style="list-style-type: none">- Changes to planned statistical analyses for efficacy evaluation, notably: optimisation of statistical methodology in particular with regard to comprehensive and efficient hypothesis testing; consideration of subject reported tinnitus loudness and annoyance as co-primary endpoints to be tested in the confirmative sense; consideration of potential efficacy differences between unilateral tinnitus and one side treated bilateral tinnitus in the general concept for evaluation; additional secondary analyses, specifically subgroup analyses for efficacy endpoints.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported