



Clinical trial results: Efficacy and Safety of AM-101 in the Treatment of Acute Peripheral Tinnitus 3 (TACTT3)

Summary

EudraCT number	2012-004099-20
Trial protocol	HU BE DE AT GB PL ES
Global end of trial date	28 December 2017

Results information

Result version number	v1 (current)
This version publication date	04 October 2019
First version publication date	04 October 2019

Trial information

Trial identification

Sponsor protocol code	AM-101-CL-12-02
-----------------------	-----------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02040194
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Auris Medical AG
Sponsor organisation address	Dornacherstr. 210, Basel, Switzerland, 4053
Public contact	Thomas Meyer, Auris Medical AG, +41 61201 1350, hear@aurismedical.com
Scientific contact	Thomas Meyer, Auris Medical AG, +41 61201 1350, 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	18 May 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 December 2017
Global end of trial reached?	Yes
Global end of trial date	28 December 2017
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 and confirmation of the efficacy of repeated intratympanic AM 101 injections in the treatment of acute peripheral tinnitus.

The study consisted of 2 strata based on time from tinnitus onset to start of treatment:

- Stratum A: onset up to 3 month (acute persistent peripheral tinnitus)
- Stratum B: onset >3 - 12 months (post-acute persistent peripheral tinnitus)

After an interim analysis, the inclusion criterium for Stratum B subjects was adapted. Please refer to section "substantial protocol amendments", 26 Mar 2015.

Furthermore a long term safety follow-up was performed. In an open label extension study, safety of continued repeated AM-101 injections was assessed in subjects who wanted to roll-over. Please refer to the AMPACT2 (2013-001527-39) database entry.

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	31 October 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Regulatory reason, Safety
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 133
Country: Number of subjects enrolled	Spain: 17
Country: Number of subjects enrolled	United Kingdom: 65
Country: Number of subjects enrolled	Austria: 17
Country: Number of subjects enrolled	Belgium: 68
Country: Number of subjects enrolled	France: 67
Country: Number of subjects enrolled	Germany: 266
Country: Number of subjects enrolled	Hungary: 93
Country: Number of subjects enrolled	Switzerland: 12

Worldwide total number of subjects	738
EEA total number of subjects	726

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)	703
From 65 to 84 years	35
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 83 sites were initiated in Austria, Belgium, France, Germany, Hungary, Poland, Switzerland, United Kingdom, and Spain. In total, 75 sites screened each at least 1 subject and 72 sites randomized subjects to treatment.

Pre-assignment

Screening details:

Main inclusion criteria: 18 to 75 years, with documented persistent subjective peripheral tinnitus (unilateral or bilateral) following traumatic cochlear injury (acute acoustic trauma, blast trauma, middle ear surgery, inner ear barotrauma, tympanic membrane trauma) or otitis media (OM)

893 were enrolled, of those 741 randomised and 738 treated.

Period 1

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

Blinding implementation details:

In particular, the study drug was of the same appearance for AM-101 and placebo and revealed no differences during or following injection, neither to the Investigator, nor to the subject. None of the Investigators was aware of the randomization schedule.

Arms

Are arms mutually exclusive?	Yes
Arm title	Stratum A - AM-101

Arm description:

Stratum A was based on time from tinnitus onset to start of treatment of up to 3 month.

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 administration of AM-101 0.87 mg/mL gel (0.25 mL) within 5 days (D0-D4)). In case of eligible bilateral tinnitus subjects, both ears were treated.

Arm title	Stratum A - Placebo
------------------	---------------------

Arm description:

Stratum A was based on time from tinnitus onset to start of treatment of up to 3 month.

Arm type	Experimental
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 administration of placebo gel (0.25 mL) 5 days (D0-D4). In case of eligible bilateral tinnitus subjects, both ears were treated.

Arm title	Stratum B - AM-101
Arm description: Stratum B contained subjects whose tinnitus onset happend >3-12 months before treatment.	
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 administration of AM-101 0.87 mg/mL gel (0.25 mL) within 5 days (D0-D4). In case of eligible bilateral tinnitus subjects, both ears were treated.

Arm title	Stratum B - Placebo
Arm description: Stratum B contained subjects whose tinnitus onset happend >3-12 months before treatment.	
Arm type	Experimental
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 administration of placebo gel (0.25 mL) within 5 days (D0-D4). In case of eligible bilateral tinnitus subjects, both ears were treated.

Number of subjects in period 1	Stratum A - AM-101	Stratum A - Placebo	Stratum B - AM-101
Started	221	149	221
Completed	216	142	216
Not completed	5	7	5
Consent withdrawn by subject	3	2	5
subject met exclusion criteria	1	-	-
Adverse event, non-fatal	-	1	-
Unforeseen business trips	-	1	-
Lost to follow-up	1	2	-
Subject did not want to continue the study	-	-	-
Subject started other therapy for tinnitus	-	1	-

Number of subjects in period 1	Stratum B - Placebo
Started	147
Completed	143
Not completed	4
Consent withdrawn by subject	2
subject met exclusion criteria	-

Adverse event, non-fatal	1
Unforeseen business trips	-
Lost to follow-up	-
Subject did not want to continue the study	1
Subject started other therapy for tinnitus	-

Baseline characteristics

Reporting groups

Reporting group title	Stratum A - AM-101
Reporting group description:	
Stratum A was based on time from tinnitus onset to start of treatment of up to 3 month.	
Reporting group title	Stratum A - Placebo
Reporting group description:	
Stratum A was based on time from tinnitus onset to start of treatment of up to 3 month.	
Reporting group title	Stratum B - AM-101
Reporting group description:	
Stratum B contained subjects whose tinnitus onset happend >3-12 months before treatment.	
Reporting group title	Stratum B - Placebo
Reporting group description:	
Stratum B contained subjects whose tinnitus onset happend >3-12 months before treatment.	

Reporting group values	Stratum A - AM-101	Stratum A - Placebo	Stratum B - AM-101
Number of subjects	221	149	221
Age categorical Units: Subjects			
Adults (18-64 years)	208	144	209
From 65-84 years	13	5	12
Age continuous Units: years			
arithmetic mean	41.6	40.7	41.1
standard deviation	± 12.89	± 18.75	± 13.37
Gender categorical Units: Subjects			
Female	62	42	54
Male	159	107	167

Reporting group values	Stratum B - Placebo	Total	
Number of subjects	147	738	
Age categorical Units: Subjects			
Adults (18-64 years)	142	703	
From 65-84 years	5	35	
Age continuous Units: years			
arithmetic mean	42.9	-	
standard deviation	± 12.28		
Gender categorical Units: Subjects			
Female	49	207	
Male	98	531	

End points

End points reporting groups

Reporting group title	Stratum A - AM-101
Reporting group description: Stratum A was based on time from tinnitus onset to start of treatment of up to 3 month.	
Reporting group title	Stratum A - Placebo
Reporting group description: Stratum A was based on time from tinnitus onset to start of treatment of up to 3 month.	
Reporting group title	Stratum B - AM-101
Reporting group description: Stratum B contained subjects whose tinnitus onset happend >3-12 months before treatment.	
Reporting group title	Stratum B - Placebo
Reporting group description: Stratum B contained subjects whose tinnitus onset happend >3-12 months before treatment.	

Primary: Improvement in TFI total score from baseline to FUV3

End point title	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). The primary efficacy analysis was performed for Stratum A. However, the exploratory efficacy analysis is as well presented for Statrum B. The stratum B population was adapted after the interim analysis. Please refer to the first amendment in section "substantial protocol amendments".	
End point type	Primary
End point timeframe: Improvement in TFI total score from baseline to FUV3 (Day 84)	

End point values	Stratum A - AM-101	Stratum A - Placebo	Stratum B - AM-101	Stratum B - Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	209	140	122	83
Units: Total score of 25 questions				
least squares mean (confidence interval 95%)	10.95 (7.79 to 14.11)	12.44 (8.98 to 15.9)	6.48 (2.08 to 10.88)	8.23 (3.56 to 12.9)

Statistical analyses

Statistical analysis title	Improvement TFI total score at FUV3 - Stratum A
Comparison groups	Stratum A - AM-101 v Stratum A - Placebo

Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.42
Method	Mixed models analysis

Statistical analysis title	Improvement TFI total score at FUV3 - Stratum B
Statistical analysis description: Stratum B analysis was of explorative nature	
Comparison groups	Stratum B - AM-101 v Stratum B - Placebo
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.43
Method	Mixed models analysis

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	Stratum A - AM-101	Stratum A - Placebo	Stratum B - AM-101	Stratum B - Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	216	144	217	146
Units: number subjects	8	8	12	19

Statistical analyses

Statistical analysis title	Strat A: Deterioration of hearing (air conduction)
Comparison groups	Stratum A - AM-101 v Stratum A - Placebo

Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.44
Method	Fisher exact

Statistical analysis title	Strat B: Deterioration of hearing (air conduction)
Comparison groups	Stratum B - AM-101 v Stratum B - Placebo
Number of subjects included in analysis	363
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02 ^[1]
Method	Fisher exact

Notes:

[1] - there was a significantly lower incidence of AM-101-treated subjects with deterioration of hearing compared to placebo-treated subjects

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline to end of study at all visits.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	20.1
--------------------	------

Reporting groups

Reporting group title	Stratum A - AM-101
-----------------------	--------------------

Reporting group description:

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

Stratum A was based on time from tinnitus onset to start of treatment of up to 3 month.

Reporting group title	Stratum A - Placebo
-----------------------	---------------------

Reporting group description:

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

Stratum A was based on time from tinnitus onset to start of treatment of up to 3 month.

Reporting group title	Stratum B - AM-101
-----------------------	--------------------

Reporting group description:

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

Stratum B contained subjects whose tinnitus onset happend >3-12 months before treatment.

Reporting group title	Stratum B - Placebo
-----------------------	---------------------

Reporting group description:

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

Stratum B contained subjects whose tinnitus onset happend >3-12 months before treatment.

Serious adverse events	Stratum A - AM-101	Stratum A - Placebo	Stratum B - AM-101
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 221 (1.36%)	3 / 149 (2.01%)	4 / 221 (1.81%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Subdural haematoma			
subjects affected / exposed	1 / 221 (0.45%)	0 / 149 (0.00%)	0 / 221 (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
Radius fracture			
subjects affected / exposed	0 / 221 (0.00%)	0 / 149 (0.00%)	1 / 221 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

Headache			
subjects affected / exposed	0 / 221 (0.00%)	1 / 149 (0.67%)	0 / 221 (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
Paraesthesia			
subjects affected / exposed	0 / 221 (0.00%)	0 / 149 (0.00%)	1 / 221 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Spermatocele			
subjects affected / exposed	0 / 221 (0.00%)	1 / 149 (0.67%)	0 / 221 (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
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 221 (0.45%)	0 / 149 (0.00%)	0 / 221 (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
Inguinal hernia			
subjects affected / exposed	0 / 221 (0.00%)	0 / 149 (0.00%)	1 / 221 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Nasal obstruction			
subjects affected / exposed	1 / 221 (0.45%)	0 / 149 (0.00%)	0 / 221 (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			
Anxiety			
subjects affected / exposed	0 / 221 (0.00%)	0 / 149 (0.00%)	0 / 221 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Completed suicide			

subjects affected / exposed	0 / 221 (0.00%)	0 / 149 (0.00%)	0 / 221 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 221 (0.00%)	1 / 149 (0.67%)	0 / 221 (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
Pneumonia			
subjects affected / exposed	0 / 221 (0.00%)	0 / 149 (0.00%)	0 / 221 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 221 (0.00%)	0 / 149 (0.00%)	1 / 221 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 221 (0.00%)	0 / 149 (0.00%)	0 / 221 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device failure			
subjects affected / exposed	0 / 221 (0.00%)	0 / 149 (0.00%)	0 / 221 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Stratum B - Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 147 (2.04%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Injury, poisoning and procedural complications			
Subdural haematoma			

subjects affected / exposed	0 / 147 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Radius fracture			
subjects affected / exposed	0 / 147 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 147 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Paraesthesia			
subjects affected / exposed	0 / 147 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Spermatocele			
subjects affected / exposed	0 / 147 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 147 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia			
subjects affected / exposed	0 / 147 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Nasal obstruction			

subjects affected / exposed	0 / 147 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Completed suicide			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 147 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	0 / 147 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tonsillitis			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device failure			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Stratum A - AM-101	Stratum A - Placebo	Stratum B - AM-101
Total subjects affected by non-serious adverse events			
subjects affected / exposed	96 / 221 (43.44%)	75 / 149 (50.34%)	122 / 221 (55.20%)
Investigations			
Blood triglycerides increased			
subjects affected / exposed	3 / 221 (1.36%)	3 / 149 (2.01%)	0 / 221 (0.00%)
occurrences (all)	3	3	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 221 (0.45%)	3 / 149 (2.01%)	0 / 221 (0.00%)
occurrences (all)	1	3	0
Headache			
subjects affected / exposed	18 / 221 (8.14%)	13 / 149 (8.72%)	27 / 221 (12.22%)
occurrences (all)	18	13	27
Ear and labyrinth disorders			
Ear discomfort	Additional description: Occurrences is equal to subjects affected.		
subjects affected / exposed	17 / 221 (7.69%)	7 / 149 (4.70%)	24 / 221 (10.86%)
occurrences (all)	17	7	24
Ear pain			
subjects affected / exposed	17 / 221 (7.69%)	6 / 149 (4.03%)	18 / 221 (8.14%)
occurrences (all)	17	6	18
Hypoacusis			
subjects affected / exposed	13 / 221 (5.88%)	9 / 149 (6.04%)	27 / 221 (12.22%)
occurrences (all)	13	9	27
Tinnitus			
subjects affected / exposed	4 / 221 (1.81%)	7 / 149 (4.70%)	10 / 221 (4.52%)
occurrences (all)	4	7	10
Otorrhoea			
subjects affected / exposed	0 / 221 (0.00%)	0 / 149 (0.00%)	0 / 221 (0.00%)
occurrences (all)	0	0	0
Vertigo			

subjects affected / exposed occurrences (all)	0 / 221 (0.00%) 0	0 / 149 (0.00%) 0	6 / 221 (2.71%) 6
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	0 / 221 (0.00%) 0	0 / 149 (0.00%) 0	2 / 221 (0.90%) 2
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	0 / 221 (0.00%) 0	3 / 149 (2.01%) 3	2 / 221 (0.90%) 2
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	10 / 221 (4.52%) 10	9 / 149 (6.04%) 9	25 / 221 (11.31%) 25
Pharyngitis subjects affected / exposed occurrences (all)	2 / 221 (0.90%) 2	3 / 149 (2.01%) 3	0 / 221 (0.00%) 0
Rhinitis subjects affected / exposed occurrences (all)	0 / 221 (0.00%) 0	0 / 149 (0.00%) 0	5 / 221 (2.26%) 5

Non-serious adverse events	Stratum B - Placebo		
Total subjects affected by non-serious adverse events subjects affected / exposed	71 / 147 (48.30%)		
Investigations Blood triglycerides increased subjects affected / exposed occurrences (all)	0 / 147 (0.00%) 0		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	0 / 147 (0.00%) 0		
Headache subjects affected / exposed occurrences (all)	14 / 147 (9.52%) 14		
Ear and labyrinth disorders Ear discomfort	Additional description: Occurrences is equal to subjects affected.		

subjects affected / exposed	16 / 147 (10.88%)		
occurrences (all)	16		
Ear pain			
subjects affected / exposed	19 / 147 (12.93%)		
occurrences (all)	19		
Hypoacusis			
subjects affected / exposed	15 / 147 (10.20%)		
occurrences (all)	15		
Tinnitus			
subjects affected / exposed	3 / 147 (2.04%)		
occurrences (all)	3		
Otorrhoea			
subjects affected / exposed	4 / 147 (2.72%)		
occurrences (all)	4		
Vertigo			
subjects affected / exposed	2 / 147 (1.36%)		
occurrences (all)	2		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	3 / 147 (2.04%)		
occurrences (all)	3		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 147 (2.04%)		
occurrences (all)	3		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	13 / 147 (8.84%)		
occurrences (all)	13		
Pharyngitis			
subjects affected / exposed	0 / 147 (0.00%)		
occurrences (all)	0		
Rhinitis			
subjects affected / exposed	2 / 147 (1.36%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 March 2015	The study protocol has been revised as a result of the pre-specified interim analysis for Stratum B. Stratum B was the exploratory cohort of patients with tinnitus onset >3 - 12 months. The pre-specified futility threshold was not reached, however the IDMC recommended to continue enrolment into Stratum B preferably with early onset (4-6 months) with unilateral tinnitus. Stratum B continued enrolment with patients whose tinnitus onset was between >3 and 6 months. Stratum A was not affected and remained unchanged.
28 September 2016	The study protocol had been revised as a result of the analysis of the phase 3 TACTT2 sister study which was conducted mainly in North America. The TLQ showed a lower sensitivity than TFI. This result was unexpected and points to a design issue relating to the frequency of TLQ assessment in TACTT2. The sponsor did elevate the TFI from key secondary to alternate primary efficacy endpoint, with the trial still blinded. Furthermore it was planned to recruit 60 more subjects in each Stratum A and B in order to enhance the trial's statistical power.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported