# 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 | Safety, Regulatory reason |
| 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<br>Units: Subjects | | | |
| Adults (18-64 years) | 208 | 144 | 209 |
| From 65-84 years | 13 | 5 | 12 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 41.6 | 40.7 | 41.1 |
| standard deviation | ± 12.89 | ± 18.75 | ± 13.37 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 62 | 42 | 54 |
| Male | 159 | 107 | 167 |

| Reporting group values | Stratum B - Placebo | Total | |
|---|---|---|---|
| Number of subjects | 147 | 738 | |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 142 | 703 | |
| From 65-84 years | 5 | 35 | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 42.9 | | |
| standard deviation | ± 12.28 | - | |
| Gender categorical<br>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.<br>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).<br><br>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.<br>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: Occurences 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 | 0 / 221 (0.00%) | 0 / 149 (0.00%) | 6 / 221 (2.71%) |
| occurrences (all) | 0 | 0 | 6 |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 0 / 221 (0.00%) | 0 / 149 (0.00%) | 2 / 221 (0.90%) |
| occurrences (all) | 0 | 0 | 2 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 221 (0.00%) | 3 / 149 (2.01%) | 2 / 221 (0.90%) |
| occurrences (all) | 0 | 3 | 2 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 10 / 221 (4.52%) | 9 / 149 (6.04%) | 25 / 221 (11.31%) |
| occurrences (all) | 10 | 9 | 25 |
| Pharyngitis | | | |
| subjects affected / exposed | 2 / 221 (0.90%) | 3 / 149 (2.01%) | 0 / 221 (0.00%) |
| occurrences (all) | 2 | 3 | 0 |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 221 (0.00%) | 0 / 149 (0.00%) | 5 / 221 (2.26%) |
| occurrences (all) | 0 | 0 | 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 | 0 / 147 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | | |
| occurrences (all) | 0 | | |
| Headache | | | |
| subjects affected / exposed | 14 / 147 (9.52%) | | |
| occurrences (all) | 14 | | |
| Ear and labyrinth disorders | | | |
| Ear discomfort | Additional description: Occurences is equal to subjects affected. | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed<br>occurrences (all) | 16 / 147 (10.88%)<br>16 | | |
| Ear pain<br>subjects affected / exposed<br>occurrences (all) | 19 / 147 (12.93%)<br>19 | | |
| Hypoacusis<br>subjects affected / exposed<br>occurrences (all) | 15 / 147 (10.20%)<br>15 | | |
| Tinnitus<br>subjects affected / exposed<br>occurrences (all) | 3 / 147 (2.04%)<br>3 | | |
| Otorrhoea<br>subjects affected / exposed<br>occurrences (all) | 4 / 147 (2.72%)<br>4 | | |
| Vertigo<br>subjects affected / exposed<br>occurrences (all) | 2 / 147 (1.36%)<br>2 | | |
| Gastrointestinal disorders<br>Nausea<br>subjects affected / exposed<br>occurrences (all) | 3 / 147 (2.04%)<br>3 | | |
| Psychiatric disorders<br>Anxiety<br>subjects affected / exposed<br>occurrences (all) | 3 / 147 (2.04%)<br>3 | | |
| Infections and infestations<br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all) | 13 / 147 (8.84%)<br>13 | | |
| Pharyngitis<br>subjects affected / exposed<br>occurrences (all) | 0 / 147 (0.00%)<br>0 | | |
| Rhinitis<br>subjects affected / exposed<br>occurrences (all) | 2 / 147 (1.36%)<br>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.<br>Stratum B continued enrolment with patients whose tinnitus onset was between >3 and 6 months.<br>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.<br>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