



Clinical trial results: Efficacy and Safety of AM-101 in the Treatment of Acute Peripheral Tinnitus 2 (TACTT2)

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2013-005587-26 |
| Trial protocol | CZ |
| Global end of trial date | 22 June 2016 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 |
| This version publication date | 21 December 2017 |
| First version publication date | 21 December 2017 |

Trial information

Trial identification

| | |
|-----------------------|-----------------|
| Sponsor protocol code | AM-101-CL-12-01 |
|-----------------------|-----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01803646 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Auris Medical Inc. |
| Sponsor organisation address | 500 North Michigan Avenue, Suite 600, Chicago, Illinois, United States, 60611 |
| Public contact | Thomas Meyer, Auris Medical Inc, +41 612011350, hear@aurismedical.com |
| Scientific contact | Thomas Meyer, Auris Medical Inc, +41 612011350, hear@aurismedical.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 23 November 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 22 June 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 22 June 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is the evaluation and confirmation of the efficacy of repeated i.t. AM-101 injections in the treatment of acute peripheral tinnitus

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 | 24 February 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Czech Republic: 64 |
| Country: Number of subjects enrolled | Canada: 34 |
| Country: Number of subjects enrolled | Israel: 3 |
| Country: Number of subjects enrolled | Korea, Republic of: 27 |
| Country: Number of subjects enrolled | Turkey: 11 |
| Country: Number of subjects enrolled | United States: 204 |
| Worldwide total number of subjects | 343 |
| EEA total number of subjects | 64 |

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) | 313 |
| From 65 to 84 years | 30 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

A total of 86 sites were initiated in Canada, the United States, the Czech Republic, Israel, Turkey and Republic of South Korea. In total, 69 sites screened each at least 1 subject and 64 sites randomized subjects for treatment.

Pre-assignment

Screening details:

The study consisted of a screening period (Day [D] -14 to D0). 478 subjects had been assessed for eligibility, of which 135 have been excluded for the following reasons:

- not meeting inclusion criteria (n=98)
- declined to participate (n=30)
- other reasons (n=7)

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, Investigator, Monitor, Data analyst |

Blinding implementation details:

The Sponsor, Investigators as well as the subjects were blinded regarding the dose administered during the study. In particular, the gel formulation was of the same appearance for AM-101 than the Placebo and revealed no differences during or following injection, neither to the Investigator, nor to the subject.

Arms

| | |
|------------------------------|-----------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | AM-101 0.87 mg/mL gel |

Arm description:

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

| | |
|--|------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Esketamine hydrochloride gel |
| Investigational medicinal product code | AM-101 |
| Other name | |
| Pharmaceutical forms | Gel for injection |
| Routes of administration | Intratympanic use |

Dosage and administration details:

Three intratympanic administrations of AM-101 0.87 mg/mL (0.25 mL). In case of eligible bilateral tinnitus subjects, both ears were treated.

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

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

| | |
|--|-------------------|
| 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:

Three intratympanic administrations of AM-101 0 mg/mL (0.25 mL). In case of eligible bilateral tinnitus subjects, both ears were treated.

| Number of subjects in period 1 | AM-101 0.87 mg/mL gel | Placebo |
|---------------------------------------|-----------------------|---------|
| Started | 204 | 139 |
| Completed | 187 | 129 |
| Not completed | 17 | 10 |
| Randomization error | 1 | 2 |
| Consent withdrawn by subject | 9 | 6 |
| Adverse event, non-fatal | 1 | 1 |
| Lost to follow-up | 5 | 1 |
| Protocol deviation | 1 | - |

Baseline characteristics

Reporting groups

| | |
|---|-----------------------|
| Reporting group title | AM-101 0.87 mg/mL gel |
| Reporting group description: Three intratympanic administration of AM-101 0.87 mg/mL gel within 5 days (D0-D4) | |
| Reporting group title | Placebo |
| Reporting group description: Three intratympanic administration of placebo gel within 5 days (D0-D4). | |

| Reporting group values | AM-101 0.87 mg/mL gel | Placebo | Total |
|---------------------------------------|-----------------------|---------|-------|
| Number of subjects | 204 | 139 | 343 |
| Age categorical Units: Subjects | | | |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 188 | 125 | 313 |
| From 65-84 years | 16 | 14 | 30 |
| Age continuous Units: years | | | |
| arithmetic mean | 43.4 | 44.2 | |
| standard deviation | ± 14.6 | ± 15.2 | - |
| Gender categorical Units: Subjects | | | |
| Female | 43 | 37 | 80 |
| Male | 161 | 102 | 263 |

Subject analysis sets

| | |
|----------------------------|--------------------|
| Subject analysis set title | Valid for Safety |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

This analysis set included all subjects who were treated with at least 1 intratympanic injection of either AM-101 or placebo. It was used as a general analysis set for safety and tolerability data. Comprises 336 subjects of 343 enrolled subjects.

| | |
|----------------------------|--------------------|
| Subject analysis set title | Valid for Efficacy |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

This analysis set was defined based on the Intention to Treat principle. It was used as the primary set for efficacy evaluation. It includes all subjects who:

- were treated with at least 1 intratympanic injection of either AM-101 or placebo
- had a valid TLQ (NRSLoudest) rating at Baseline and at least 1 valid post-Baseline TLQ (NRSLoudest) rating or had a valid TFI rating at Baseline and at least 1 valid post-Baseline TFI rating.

| Reporting group values | Valid for Safety | Valid for Efficacy | |
|------------------------------------|------------------|--------------------|--|
| Number of subjects | 336 | 326 | |
| Age categorical Units: Subjects | | | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 306 | 297 | |

| | | | |
|------------------|----|----|--|
| From 65-84 years | 30 | 29 | |
|------------------|----|----|--|

| | | | |
|---|---------------|---------------|--|
| Age continuous Units: years arithmetic mean standard deviation | ± | ± | |
| Gender categorical Units: Subjects | | | |
| Female | 78 | 78 | |
| Male | 258 | 248 | |

End points

End points reporting groups

| | |
|--|-----------------------|
| Reporting group title | AM-101 0.87 mg/mL gel |
| Reporting group description: Three intratympanic administration of AM-101 0.87 mg/mL gel within 5 days (D0-D4) | |
| Reporting group title | Placebo |
| Reporting group description: Three intratympanic administration of placebo gel within 5 days (D0-D4). | |
| Subject analysis set title | Valid for Safety |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: This analysis set included all subjects who were treated with at least 1 intratympanic injection of either AM-101 or placebo. It was used as a general analysis set for safety and tolerability data. Comprises 336 subjects of 343 enrolled subjects. | |
| Subject analysis set title | Valid for Efficacy |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: This analysis set was defined based on the Intention to Treat principle. It was used as the primary set for efficacy evaluation. It includes all subjects who: <ul style="list-style-type: none">• were treated with at least 1 intratympanic injection of either AM-101 or placebo• had a valid TLQ (NRSLoudest) rating at Baseline and at least 1 valid post-Baseline TLQ (NRSLoudest) rating or had a valid TFI rating at Baseline and at least 1 valid post-Baseline TFI rating. | |

Primary: Efficacy: Patient-reported TLQ Improvement from Baseline to FUV3

| | |
|---|--|
| End point title | Efficacy: Patient-reported TLQ Improvement from Baseline to FUV3 |
| End point description: Improvement in patient-reported tinnitus loudness TLQ NRSLoudest from baseline to FUV3. | |
| End point type | Primary |
| End point timeframe: Baseline (TV1) up to end of study (FUV3) | |

| End point values | AM-101 0.87 mg/mL gel | Placebo | | |
|--|-----------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 195 | 129 | | |
| Units: Numerical rating scale (0-10) | | | | |
| least squares mean (confidence interval 95%) | 0.80 (0.51 to 1.08) | 0.63 (0.38 to 0.87) | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Improvement in tinnitus loudness from baseline |
| Comparison groups | AM-101 0.87 mg/mL gel v Placebo |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 324 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.32 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.17 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.51 |
| upper limit | 0.17 |

Primary: Co-Primary Efficacy: Improvement in TFI total score from baseline to FUV3

| | |
|-----------------|---|
| End point title | Co-Primary Efficacy: 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).

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Improvement in TFI total score from baseline to FUV3

| | | | | |
|--|-----------------------|-------------------|--|--|
| End point values | AM-101 0.87 mg/mL gel | Placebo | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 180 | 121 | | |
| Units: Total score of 25 questions | | | | |
| least squares mean (confidence interval 95%) | 10.4 (6.5 to 14.3) | 9.6 (5.9 to 13.3) | | |

Statistical analyses

| | |
|---|-------------------------------------|
| Statistical analysis title | Improvement TFI total score at FUV3 |
| Comparison groups | AM-101 0.87 mg/mL gel v Placebo |
| Number of subjects included in analysis | 301 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.63 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.79 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4 |
| upper limit | 2.4 |

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 | AM-101 0.87 mg/mL gel | Placebo | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 193 | 130 | | |
| Units: number subjects | | | | |
| Air conduction | 12 | 9 | | |
| Bone conduction | 3 | 4 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Deterioration of hearing for air conduction |
| Comparison groups | AM-101 0.87 mg/mL gel v Placebo |
| Number of subjects included in analysis | 323 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.821 |
| Method | Fisher exact |

| | |
|-----------------------------------|--|
| Statistical analysis title | Deterioration of hearing for bone conduction |
| Comparison groups | AM-101 0.87 mg/mL gel v Placebo |

| | |
|---|---------------|
| Number of subjects included in analysis | 323 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 1 |
| Method | Fisher exact |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline to end of study at all visits.

Adverse event reporting additional description:

Assessed by investigator at all visits.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------|
| Reporting group title | AM-101 |
|-----------------------|--------|

Reporting group description: -

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description: -

| Serious adverse events | AM-101 | Placebo | |
|---|-----------------|-----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 201 (2.49%) | 1 / 135 (0.74%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Lower limb fracture | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 135 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tendon rupture | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 135 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 135 (0.74%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Generalised tonic-clonic seizure | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 135 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Mental disorder | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 135 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 135 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | AM-101 | Placebo | |
|---|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 90 / 201 (44.78%) | 46 / 135 (34.07%) | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 10 / 201 (4.98%) | 1 / 135 (0.74%) | |
| occurrences (all) | 10 | 1 | |
| Headache | | | |
| subjects affected / exposed | 11 / 201 (5.47%) | 6 / 135 (4.44%) | |
| occurrences (all) | 11 | 6 | |
| General disorders and administration site conditions | | | |
| Injection site pain | | | |
| subjects affected / exposed | 5 / 201 (2.49%) | 1 / 135 (0.74%) | |
| occurrences (all) | 5 | 1 | |
| Ear and labyrinth disorders | | | |
| Ear discomfort | | | |
| subjects affected / exposed | 14 / 201 (6.97%) | 8 / 135 (5.93%) | |
| occurrences (all) | 14 | 8 | |
| Ear pain | | | |

| | | | |
|--|------------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 16 / 201 (7.96%) 16 | 10 / 135 (7.41%) 10 | |
| Hypoacusis subjects affected / exposed occurrences (all) | 8 / 201 (3.98%) 8 | 4 / 135 (2.96%) 4 | |
| Tinnitus subjects affected / exposed occurrences (all) | 8 / 201 (3.98%) 8 | 5 / 135 (3.70%) 5 | |
| Tympanic membrane perforation subjects affected / exposed occurrences (all) | 5 / 201 (2.49%) 5 | 4 / 135 (2.96%) 4 | |
| Vertigo subjects affected / exposed occurrences (all) | 2 / 201 (1.00%) 2 | 4 / 135 (2.96%) 4 | |
| Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) | 4 / 201 (1.99%) 4 | 2 / 135 (1.48%) 2 | |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 7 / 201 (3.48%) 7 | 1 / 135 (0.74%) 1 | |
| Insomnia subjects affected / exposed occurrences (all) | 4 / 201 (1.99%) 4 | 0 / 135 (0.00%) 0 | |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 6 / 201 (2.99%) 6 | 4 / 135 (2.96%) 4 | |
| Sinusitis subjects affected / exposed occurrences (all) | 4 / 201 (1.99%) 4 | 0 / 135 (0.00%) 0 | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 5 / 201 (2.49%) 5 | 2 / 135 (1.48%) 2 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/28608739>