



Clinical trial results: Efficacy and Safety of AM-111 in the Treatment of Acute Inner Ear Hearing Loss (HEALOS)

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2013-002077-21 |
| Trial protocol | BG HU ES DE CZ |
| Global end of trial date | 28 September 2017 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 15 October 2020 |
| First version publication date | 15 October 2020 |

Trial information

Trial identification

| | |
|-----------------------|-----------------|
| Sponsor protocol code | AM-111-CL-13-01 |
|-----------------------|-----------------|

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 | Dornacherstrasse 210, Basel, Switzerland, 4053 |
| Public contact | Thomas Meyer, Auris Medical AG, +41 61 201 13 50, hear@aurismedical.com |
| Scientific contact | Thomas Meyer, Auris Medical AG, +41 61 201 13 50, 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 | 13 March 2018 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 28 September 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Confirmation of the efficacy of AM-111 in the recovery of severe to profound idiopathic sudden sensorineural hearing loss (ISSNHL).

Protection of trial subjects:

The trial was performed in compliance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) Guidelines, and in accordance with the current version of the Declaration of Helsinki.

Background therapy:

Optional reserve therapy - In case of insufficient hearing recovery at Day 7, the option of a treatment course of oral corticosteroids was offered as reserve therapy to subjects, unless medically contraindicated.

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 13 November 2015 |
| 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 | Thailand: 47 |
| Country: Number of subjects enrolled | Turkey: 5 |
| Country: Number of subjects enrolled | Poland: 30 |
| Country: Number of subjects enrolled | Bulgaria: 41 |
| Country: Number of subjects enrolled | Czech Republic: 19 |
| Country: Number of subjects enrolled | Germany: 19 |
| Country: Number of subjects enrolled | Hungary: 8 |
| Country: Number of subjects enrolled | Russian Federation: 47 |
| Country: Number of subjects enrolled | Serbia: 21 |
| Country: Number of subjects enrolled | Taiwan: 19 |
| Worldwide total number of subjects | 256 |
| EEA total number of subjects | 117 |

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) | 251 |
| From 65 to 84 years | 5 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Due to the acute nature of the disease and the short time window for treatment, potential subjects were recruited in emergency units and by ENT professionals.

Pre-assignment

Screening details:

A total of 258 subjects have been screened. After 2 screening failures, 256 subjects were randomized into the study.

Period 1

| | |
|------------------------------|--|
| Period 1 title | Whole study (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 Investigators and subjects were blinded regarding the dose administered during the study. This applied also to the trial personnel at the Sponsor and the clinical research organization (CRO) except for designated unblinded staff at the CRO. The gel formulation was of the same appearance for AM-111 0.4 and 0.8 mg/mL and placebo, with no differences apparent to Investigator or subject during or following injection. None of the Investigators were aware of the randomization schedule.

Arms

| | |
|--|-------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo |
| Arm description: - | |
| Arm type | Placebo |
| Investigational medicinal product name | Placebo gel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Gel for injection |
| Routes of administration | Intratympanic use |

Dosage and administration details:

Injection of 0.25 mL study drug (AM-111 0.4 mg/mL or 0.8 mg/mL or placebo) into the eligible ear at the treatment visit.

| | |
|--|-------------------|
| Arm title | AM-111 0.4 mg/mL |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | AM-111 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Gel for injection |
| Routes of administration | Intratympanic use |

Dosage and administration details:

Injection of 0.25 mL study drug (AM-111 0.4 mg/mL or 0.8 mg/mL or placebo) into the eligible ear at the treatment visit.

| | |
|--------------------|------------------|
| Arm title | AM-111 0.8 mg/mL |
| Arm description: - | |
| Arm type | Experimental |

| | |
|--|-------------------|
| Investigational medicinal product name | AM-111 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Gel for injection |
| Routes of administration | Intratympanic use |

Dosage and administration details:

Injection of 0.25 mL study drug (AM-111 0.4 mg/mL or 0.8 mg/mL or placebo) into the eligible ear at the treatment visit.

| Number of subjects in period 1 | Placebo | AM-111 0.4 mg/mL | AM-111 0.8 mg/mL |
|---------------------------------------|---------|------------------|------------------|
| Started | 85 | 85 | 86 |
| Completed | 81 | 81 | 83 |
| Not completed | 4 | 4 | 3 |
| Consent withdrawn by subject | 4 | 4 | 1 |
| Physician decision | - | - | 1 |
| Protocol deviation | - | - | 1 |

Baseline characteristics

Reporting groups

| | |
|--------------------------------|------------------|
| Reporting group title | Placebo |
| Reporting group description: - | |
| Reporting group title | AM-111 0.4 mg/mL |
| Reporting group description: - | |
| Reporting group title | AM-111 0.8 mg/mL |
| Reporting group description: - | |

| Reporting group values | Placebo | AM-111 0.4 mg/mL | AM-111 0.8 mg/mL |
|---------------------------------------|---------|------------------|------------------|
| Number of subjects | 85 | 85 | 86 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 83 | 83 | 85 |
| From 65-84 years | 2 | 2 | 1 |
| Age continuous Units: years | | | |
| arithmetic mean | 45.5 | 45.8 | 48.0 |
| standard deviation | ± 12.1 | ± 13.1 | ± 10.9 |
| Gender categorical Units: Subjects | | | |
| Female | 39 | 41 | 42 |
| Male | 46 | 44 | 44 |

| Reporting group values | Total | | |
|---------------------------------------|-------|--|--|
| Number of subjects | 256 | | |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 251 | | |
| From 65-84 years | 5 | | |
| Age continuous Units: years | | | |
| arithmetic mean | - | | |
| standard deviation | - | | |
| Gender categorical Units: Subjects | | | |
| Female | 122 | | |
| Male | 134 | | |

End points

End points reporting groups

| | |
|--------------------------------|------------------|
| Reporting group title | Placebo |
| Reporting group description: - | |
| Reporting group title | AM-111 0.4 mg/mL |
| Reporting group description: - | |
| Reporting group title | AM-111 0.8 mg/mL |
| Reporting group description: - | |

Primary: Efficacy: Improvement of PTA for all subjects

| | |
|--|---|
| End point title | Efficacy: Improvement of PTA for all subjects |
| End point description: | |
| Pure tone average (PTA) - average across the 3 most affected contiguous air conduction audiometric pure tone frequencies. Pure tone audiometry measures were performed by certified audiologists or adequately trained site staff and conducted in a sound attenuated booth/room, using standard earphones or earphone inserts. Hearing thresholds were determined by pure tone audiometry in both ears at 0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz (air conduction) in accordance with ISO standard 8253-1 and any other relevant standards. | |
| End point type | Primary |
| End point timeframe: | |
| From Baseline to follow-up visit 3 (FUV3) (Day 28) | |

| End point values | Placebo | AM-111 0.4 mg/mL | AM-111 0.8 mg/mL | |
|-------------------------------------|----------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 79 | 77 | 84 | |
| Units: Frequency | | | | |
| least squares mean (standard error) | 33.78 (\pm 2.709) | 38.44 (\pm 2.753) | 36.63 (\pm 2.614) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | PTA difference between Placebo and AM-111 0.4mg/mL |
| Comparison groups | Placebo v AM-111 0.4 mg/mL |
| Number of subjects included in analysis | 156 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2263 |
| Method | ANCOVA |
| Parameter estimate | Difference |

| | |
|---------------------|-------------|
| Confidence interval | |
| level | Other: 96 % |
| sides | 2-sided |
| lower limit | -3.28 |
| upper limit | 12.6 |

| | |
|---|--|
| Statistical analysis title | PTA difference between Placebo and AM-111 0.8mg/mL |
| Statistical analysis description: | |
| Superiority testing of Placebo vs. AM-111 0.8 mg/mL was not the primary efficacy endpoint | |
| Comparison groups | Placebo v AM-111 0.8 mg/mL |
| Number of subjects included in analysis | 163 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.448 |
| Method | ANCOVA |
| Parameter estimate | Difference |
| Confidence interval | |
| level | Other: 99 % |
| sides | 2-sided |
| lower limit | -6.89 |
| upper limit | 12.59 |

| | |
|---|---|
| Primary: Safety: Occurrence of clinically relevant hearing deterioration | |
| End point title | Safety: Occurrence of clinically relevant hearing deterioration |
| End point description: | |
| Occurrence of clinically relevant hearing deterioration (increase in air conduction hearing threshold > 10 dB at the average of any 2 contiguous test frequencies) in the treated ear from baseline to FUV3 (Day 28). | |
| End point type | Primary |
| End point timeframe: | |
| From Baseline to Follow-up Visit 3 (FUV3) (Day 28) | |

| End point values | Placebo | AM-111 0.4 mg/mL | AM-111 0.8 mg/mL | |
|-----------------------------|-----------------|------------------|------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 76 | 74 | 83 | |
| Units: Number subjects | 5 | 4 | 2 | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Difference between Placebo and AM-111 0.4 mg/mL |
| Comparison groups | Placebo v AM-111 0.4 mg/mL |
| Number of subjects included in analysis | 150 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 1 |
| Method | Fisher exact |

| | |
|---|---|
| Statistical analysis title | Difference between Placebo and AM-111 0.8 mg/mL |
| Comparison groups | Placebo v AM-111 0.8 mg/mL |
| Number of subjects included in analysis | 159 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2603 |
| Method | Fisher exact |

Post-hoc: Efficacy: Improvement of PTA for profound hearing loss subjects

| | |
|-----------------|---|
| End point title | Efficacy: Improvement of PTA for profound hearing loss subjects |
|-----------------|---|

End point description:

PTA: Pure tone average determined by air conduction audiometry.

Profound hearing loss: The post-hoc analyses were based on a commonly used classification of hearing loss severity, which separates severe from profound hearing loss at the level of 90 dB. Profound hearing loss is present when the hearing loss is equal or above 90 dB. Those subjects perceive loud sounds mainly as vibrations.

| | |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

From Baseline (Day 0) to Follow-up Visit 3 (FUV3) (Day 28)

| End point values | Placebo | AM-111 0.4 mg/mL | AM-111 0.8 mg/mL | |
|----------------------------------|-----------------|------------------|------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 34 | 35 | 30 | |
| Units: Frequency | | | | |
| arithmetic mean (standard error) | 26.78 (± 4.706) | 42.71 (± 4.645) | 37.34 (± 5.008) | |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | PTA difference between Placebo and AM-111 0.4mg/mL |
|-----------------------------------|--|

Statistical analysis description:

Post-hoc analysis with subjects that experienced a profound hearing loss.

| | |
|---|----------------------------|
| Comparison groups | AM-111 0.4 mg/mL v Placebo |
| Number of subjects included in analysis | 69 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | = 0.0176 |
| Method | ANCOVA |
| Parameter estimate | Difference |
| Confidence interval | |
| level | Other: 96 % |
| sides | 2-sided |
| lower limit | 2.2 |
| upper limit | 29.66 |

| | |
|---|--|
| Statistical analysis title | PTA difference between Placebo and AM-111 0.8mg/mL |
| Comparison groups | Placebo v AM-111 0.8 mg/mL |
| Number of subjects included in analysis | 64 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | = 0.126 |
| Method | ANCOVA |
| Parameter estimate | Difference |
| Confidence interval | |
| level | Other: 99 % |
| sides | 2-sided |
| lower limit | -7.43 |
| upper limit | 28.54 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The AE reporting for this study began at the time of signature of informed consent and ended at the last follow-up visit (FUV4).

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

Dictionary used

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

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

Reporting groups

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

Reporting group description:

2% threshold applies for subjects affected by non-serious adverse events

| | |
|-----------------------|------------------|
| Reporting group title | AM-111 0.4 mg/mL |
|-----------------------|------------------|

Reporting group description:

2% threshold applies for subjects affected by non-serious adverse events

| | |
|-----------------------|------------------|
| Reporting group title | AM-111 0.8 mg/mL |
|-----------------------|------------------|

Reporting group description:

2% threshold applies for subjects affected by non-serious adverse events

| Serious adverse events | Placebo | AM-111 0.4 mg/mL | AM-111 0.8 mg/mL |
|---|----------------|------------------|------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 85 (3.53%) | 2 / 85 (2.35%) | 2 / 86 (2.33%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Fibroadenoma of breast | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 1 / 85 (1.18%) | 0 / 86 (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 |
| Surgical and medical procedures | | | |
| Acoustic neuroma removal | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 0 / 85 (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 | | | |
| Cardiac failure congestive | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 85 (0.00%) | 0 / 85 (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 |
| Blood and lymphatic system disorders | | | |
| Polycythaemia | | | |
| subjects affected / exposed | 1 / 85 (1.18%) | 0 / 85 (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 |
| Gastrointestinal disorders | | | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 1 / 85 (1.18%) | 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 |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 1 / 85 (1.18%) | 0 / 85 (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 |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus inadequate control | | | |
| subjects affected / exposed | 1 / 85 (1.18%) | 0 / 85 (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 |

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

| Non-serious adverse events | Placebo | AM-111 0.4 mg/mL | AM-111 0.8 mg/mL |
|--|------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 29 / 85 (34.12%) | 24 / 85 (28.24%) | 22 / 86 (25.58%) |
| Investigations | | | |
| Blood pressure increased | | | |
| subjects affected / exposed | 1 / 85 (1.18%) | 2 / 85 (2.35%) | 0 / 86 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Nervous system disorders | | | |
| Headache | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 5 / 85 (5.88%) 5 | 2 / 85 (2.35%) 2 | 5 / 86 (5.81%) 7 |
| Dizziness subjects affected / exposed occurrences (all) | 1 / 85 (1.18%) 1 | 3 / 85 (3.53%) 3 | 4 / 86 (4.65%) 6 |
| General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all) | 2 / 85 (2.35%) 2 | 0 / 85 (0.00%) 0 | 1 / 86 (1.16%) 1 |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 4 / 85 (4.71%) 4 | 2 / 85 (2.35%) 3 | 5 / 86 (5.81%) 5 |
| Ear pain subjects affected / exposed occurrences (all) | 2 / 85 (2.35%) 2 | 3 / 85 (3.53%) 3 | 1 / 86 (1.16%) 1 |
| Tinnitus subjects affected / exposed occurrences (all) | 4 / 85 (4.71%) 4 | 1 / 85 (1.18%) 1 | 0 / 86 (0.00%) 0 |
| Vertigo positional subjects affected / exposed occurrences (all) | 1 / 85 (1.18%) 1 | 3 / 85 (3.53%) 3 | 1 / 86 (1.16%) 1 |
| Ear discomfort subjects affected / exposed occurrences (all) | 2 / 85 (2.35%) 2 | 1 / 85 (1.18%) 1 | 0 / 86 (0.00%) 0 |
| Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all) | 1 / 85 (1.18%) 1 | 2 / 85 (2.35%) 2 | 1 / 86 (1.16%) 1 |
| Nausea subjects affected / exposed occurrences (all) | 2 / 85 (2.35%) 2 | 0 / 85 (0.00%) 0 | 0 / 86 (0.00%) 0 |
| Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) | 2 / 85 (2.35%) 2 | 0 / 85 (0.00%) 0 | 0 / 86 (0.00%) 0 |

| | | | |
|--|---------------------|---------------------|---------------------|
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 2 / 85 (2.35%) 2 | 5 / 85 (5.88%) 5 | 1 / 86 (1.16%) 1 |
| Rhinitis subjects affected / exposed occurrences (all) | 0 / 85 (0.00%) 0 | 0 / 85 (0.00%) 0 | 3 / 86 (3.49%) 3 |

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/31083077>