



Clinical trial results:

AM-101 in the Post-Acute Treatment of Peripheral Tinnitus 2 (AMPACT2) – an open-label extension to the TACTT3 study

Summary

| | |
|--------------------------|----------------------|
| EudraCT number | 2013-001527-39 |
| Trial protocol | HU BE DE AT GB PL ES |
| Global end of trial date | 19 December 2016 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 20 June 2019 |
| First version publication date | 20 June 2019 |

Trial information

Trial identification

| | |
|-----------------------|-----------------|
| Sponsor protocol code | AM-101-CL-12-04 |
|-----------------------|-----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02040207 |
| 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 | 25 April 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 19 December 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 19 December 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 of the safety and local tolerance of up to 3 quarterly treatment cycles each with 3 repeated doses of AM-101 0.87 mg/mL in subjects previously treated in the scope of the TACTT3 study with either AM-101 0.87 mg/mL or placebo.

Subjects were followed for up to a cumulative observational period of 1 year in subjects with acute persistent peripheral tinnitus.

Subjects who completed TACTT3, could roll-over into treatment cycle 1 of this study (AMPACT2). After completion of treatment cycle 1 they were free to decide if they want to continue with treatment cycle 2. Same for treatment cycle 3.

In total 485 subjects were treated in AMPACT2 of which:

- 347 subjects participated only in the first treatment cycle,
- 66 subjects participated in the first 2 treatment cycles,
- 72 subjects completed all 3 treatment cycles.

1 subject was enrolled but not treated. It is not included in the following numbers.

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 | 07 May 2015 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 12 Months |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Poland: 92 |
| Country: Number of subjects enrolled | Spain: 17 |
| Country: Number of subjects enrolled | United Kingdom: 42 |
| Country: Number of subjects enrolled | Austria: 13 |
| Country: Number of subjects enrolled | Belgium: 43 |
| Country: Number of subjects enrolled | France: 43 |
| Country: Number of subjects enrolled | Germany: 163 |
| Country: Number of subjects enrolled | Hungary: 64 |
| Country: Number of subjects enrolled | Switzerland: 8 |

| | |
|------------------------------------|-----|
| Worldwide total number of subjects | 485 |
| EEA total number of subjects | 477 |

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) | 461 |
| From 65 to 84 years | 24 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

A total of 486 subjects were enrolled. 1 Subject was enrolled but not treated (this subject is not listed). 485 subjects were treated. Subjects were enrolled at 69 sites. Subjects could only participate if they had been previously enrolled in TACTT3.

Pre-assignment

Screening details:

Main Inclusion Criteria:

Attendance at final visit FUV3 of TACTT3 study and no study drug related or procedure related adverse event (AE) leading to treatment discontinuation in study TACTT3.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Blinding implementation details:

This study was an open-label extension study subsequent to the previous blinded, placebo controlled, randomized TACTT3 study. This study was requested by the FDA as long-term safety follow-up of repeated AM-101 injection cycles over 1 year.

Arms

| | |
|------------------------------|----------------|
| Are arms mutually exclusive? | Yes |
| Arm title | 1 Cycle AM-101 |

Arm description:

Subjects participated in 1 treatment cycle and received one round of 3 repeated doses of AM-101 gel (0.87 mg/mL) 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:

Subjects who participated only in treatment cycle 1, received three intratympanic administrations of AM-101 0.87 mg/mL (0.25 mL). In case of eligible bilateral tinnitus, both ears were treated.

| | |
|------------------|-----------------|
| Arm title | 2 Cycles AM-101 |
|------------------|-----------------|

Arm description:

Subjects that participated in 2 treatment cycles of the AMPACT2 study, received 3 repeated doses of AM-101 gel (0.87 mg/mL) within 5 days (D0 - D4) in cycle 1 and after final follow-up (D84) of cycle 1, they rolled-over to treatment cycle 2 receiving once more 3 repeated doses of AM-101 gel (0.87 mg/mL) within 5 days (D84 - D88).

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

Subjects who participated in 2 treatment cycles, received 1x three intratympanic administrations of AM-101 0.87 mg/mL (0.25 mL) within 5 days and a second time three intratympanic injections of AM-101 0.87 mg/mL within 5 days after FUV3 (D84) of treatment cycle 1.

In case of eligible bilateral tinnitus, both ears were treated.

| | |
|---|------------------------------|
| Arm title | 3 Cycles AM-101 |
| Arm description: | |
| Subjects that participated in all 3 treatment cycles of the AMPACT2 study, received 3 x 3 repeated doses of AM-101 gel (0.87 mg/mL) within 5 days. The subjects could only roll-over if they completed the final follow-up of the previous cycle and were still eligible. | |
| In cycle 1 treatment was within D0 - D4. Cycle 2 treatment within D84 - D88. And treatment for cycle 3 within D168-D172. Final follow-up after 3 treatment cycles was FUV9 (D252). | |
| 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:

Subjects who participated in all three treatment cycles, received 3 times three intratympanic administrations of AM-101 0.87 mg/mL (0.25 mL).

Please refer to arm description for details.

In case of eligible bilateral tinnitus, both ears were treated.

| Number of subjects in period 1 | 1 Cycle AM-101 | 2 Cycles AM-101 | 3 Cycles AM-101 |
|---------------------------------------|----------------|-----------------|-----------------|
| Started | 347 | 66 | 72 |
| Completed | 312 | 62 | 69 |
| Not completed | 35 | 4 | 3 |
| Exclusion criteria met | 1 | - | - |
| Consent withdrawn by subject | 14 | 3 | 1 |
| Physician decision | 1 | - | - |
| Adverse event, non-fatal | 2 | - | - |
| Lost to follow-up | 16 | 1 | 2 |
| not able to join visits | 1 | - | - |

Baseline characteristics

Reporting groups

| | |
|---|-----------------|
| Reporting group title | 1 Cycle AM-101 |
| Reporting group description: | |
| Subjects participated in 1 treatment cycle and received one round of 3 repeated doses of AM-101 gel (0.87 mg/mL) within 5 days (D0 - D4) | |
| Reporting group title | 2 Cycles AM-101 |
| Reporting group description: | |
| Subjects that participated in 2 treatment cycles of the AMPACT2 study, received 3 repeated doses of AM-101 gel (0.87 mg/mL) within 5 days (D0 - D4) in cycle 1 and after final follow-up (D84) of cycle 1, they rolled-over to treatment cycle 2 receiving once more 3 repeated doses of AM-101 gel (0.87 mg/mL) within 5 days (D84 - D88). | |
| Reporting group title | 3 Cycles AM-101 |
| Reporting group description: | |
| Subjects that participated in all 3 treatment cycles of the AMPACT2 study, received 3 x 3 repeated doses of AM-101 gel (0.87 mg/mL) within 5 days. The subjects could only roll-over if they completed the final follow-up of the previous cycle and were still eligible. | |
| In cycle 1 treatment was within D0 - D4. Cycle 2 treatment within D84 - D88. And treatment for cycle 3 within D168-D172. Final follow-up after 3 treatment cycles was FUV9 (D252). | |

| Reporting group values | 1 Cycle AM-101 | 2 Cycles AM-101 | 3 Cycles AM-101 |
|------------------------|----------------|-----------------|-----------------|
| Number of subjects | 347 | 66 | 72 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 330 | 65 | 66 |
| From 65-84 years | 17 | 1 | 6 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 41.8 | 41.8 | 43.4 |
| standard deviation | ± 12.83 | ± 11.40 | ± 12.32 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 89 | 19 | 24 |
| Male | 258 | 47 | 48 |

| Reporting group values | Total | | |
|------------------------|-------|--|--|
| Number of subjects | 485 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 461 | | |
| From 65-84 years | 24 | | |
| 85 years and over | 0 | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 132 | | |

| | | | |
|------|-----|--|--|
| Male | 353 | | |
|------|-----|--|--|

End points

End points reporting groups

| | |
|---|-----------------|
| Reporting group title | 1 Cycle AM-101 |
| Reporting group description: Subjects participated in 1 treatment cycle and received one round of 3 repeated doses of AM-101 gel (0.87 mg/mL) within 5 days (D0 - D4) | |
| Reporting group title | 2 Cycles AM-101 |
| Reporting group description: Subjects that participated in 2 treatment cycles of the AMPACT2 study, received 3 repeated doses of AM-101 gel (0.87 mg/mL) within 5 days (D0 - D4) in cycle 1 and after final follow-up (D84) of cycle 1, they rolled-over to treatment cycle 2 receiving once more 3 repeated doses of AM-101 gel (0.87 mg/mL) within 5 days (D84 - D88). | |
| Reporting group title | 3 Cycles AM-101 |
| Reporting group description: Subjects that participated in all 3 treatment cycles of the AMPACT2 study, received 3 x 3 repeated doses of AM-101 gel (0.87 mg/mL) within 5 days. The subjects could only roll-over if they completed the final follow-up of the previous cycle and were still eligible. In cycle 1 treatment was within D0 - D4. Cycle 2 treatment within D84 - D88. And treatment for cycle 3 within D168-D172. Final follow-up after 3 treatment cycles was FUV9 (D252). | |

Primary: Primary: Frequency of Subjects With a Deterioration of Hearing Threshold at Day 35 (Air Conduction)

| | |
|---|---|
| End point title | Primary: Frequency of Subjects With a Deterioration of Hearing Threshold at Day 35 (Air Conduction) |
| End point description: Valid for Safety Analysis Set was used. Air conduction: The atmospheric transmission of sound to the inner ear through the external auditory canal and via structures of the middle ear. The ability of hearing is measured in decibel (dB). The hearing threshold, is the lowest sound pressure where the subject can still perceive a sound. The endpoint deterioration of hearing threshold ≥ 15 dB in two contiguous test frequencies means that hearing worsens ≥ 15 dB in two neighboring sound frequencies. | |
| End point type | Primary |
| End point timeframe: Day 1 (TV1) to Day 35 (FUV2) of cycle 1 | |

| End point values | 1 Cycle AM-101 | 2 Cycles AM-101 | 3 Cycles AM-101 | |
|---------------------------------|--------------------|-------------------|-------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 323 ^[1] | 66 ^[2] | 72 ^[3] | |
| Units: Number subjects affected | | | | |
| number (not applicable) | 27 | 3 | 7 | |

Notes:

- [1] - Subjects who participated only in 1 treatment cycle and are valid for this endpoint.
- [2] - Subjects who received two treatment cycles and are valid for this endpoint.
- [3] - Subjects who received 3 treatment cycles and are valid for this endpoint.

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Subjects participating in 1 Cycle vs. 2 Cycles |
| Statistical analysis description: | |
| Fisher's exact test to assess if there is a difference in deterioration of hearing threshold between subjects that had only 1 treatment cycle or those that decided later to have 2 treatment cycles. The analysis is based on the deterioration of hearing detected at FUV2 for all subjects in those groups. | |
| Comparison groups | 1 Cycle AM-101 v 2 Cycles AM-101 |
| Number of subjects included in analysis | 389 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4462 |
| Method | Fisher exact |

| | |
|--|--|
| Statistical analysis title | Subjects participating in 1 Cycle vs. 3 Cycles |
| Statistical analysis description: | |
| Fisher's exact test to assess if there is a difference in deterioration of hearing threshold between subjects that had only 1 treatment cycle or those that decided later to have 3 treatment cycles. The analysis is based on the deterioration of hearing detected at FUV2 for all subjects in those groups. | |
| Comparison groups | 1 Cycle AM-101 v 3 Cycles AM-101 |
| Number of subjects included in analysis | 395 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6483 |
| Method | Fisher exact |

| | |
|--|---|
| Statistical analysis title | Subjects participating in 2 Cycles vs. 3 Cycles |
| Statistical analysis description: | |
| Fisher's exact test to assess if there is a difference in deterioration of hearing threshold between subjects that decided to participate in 2 treatment cycles or those that decided later to have 3 treatment cycles. The analysis is based on the deterioration of hearing detected at FUV2 for all subjects in those groups. | |
| Comparison groups | 2 Cycles AM-101 v 3 Cycles AM-101 |
| Number of subjects included in analysis | 138 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3302 |
| Method | Fisher exact |

Primary: Primary: Frequency of Subjects With a Deterioration of Hearing Threshold at Day 119 (Air Conduction)

| | |
|-----------------|---|
| End point title | Primary: Frequency of Subjects With a Deterioration of Hearing Threshold at Day 119 (Air Conduction) ^[4] |
|-----------------|---|

End point description:

Valid for Safety Analysis Set was used. Air conduction: The atmospheric transmission of sound to the inner ear through the external auditory canal and via structures of the middle ear. The ability of hearing is measured in decibel (dB). The hearing threshold, is the lowest sound pressure where the subject can still perceive a sound. The endpoint deterioration of hearing threshold ≥ 15 dB in two contiguous test frequencies means that hearing worsens ≥ 15 dB in two neighboring sound frequencies.

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

End point timeframe:

Day 84 (TV4) to Day 119 (FUV5) of cycle 2

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Deterioration of hearing threshold at FUV5 (Day 119) is only evaluable for subjects that participated in 2 or 3 treatment cycles. For subjects that participated only in one treatment cycle, the study had already ended after FUV3 (Day 84). Therefore, only one statistical comparison between subjects that participated in 2 vs. 3 treatment cycles, is possible.

| End point values | 2 Cycles AM-101 | 3 Cycles AM-101 | | |
|---------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 58 | 71 | | |
| Units: Number subjects affected | 5 | 4 | | |

Statistical analyses

| Statistical analysis title | Subjects participating in 2 Cycles vs. 3 Cycles |
|----------------------------|---|
|----------------------------|---|

Statistical analysis description:

Fisher's exact test to assess if there is a difference in deterioration of hearing threshold between subjects that decided to participate in 2 treatment cycle or those that decided later to have 3 treatment cycles. The analysis is based on the deterioration of hearing detected at FUV5 for all subjects in those groups.

| | |
|---|-----------------------------------|
| Comparison groups | 2 Cycles AM-101 v 3 Cycles AM-101 |
| Number of subjects included in analysis | 129 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7304 |
| Method | Fisher exact |

Primary: Primary: Frequency of Subjects With a Deterioration of Hearing Threshold at Day 203 (Air Conduction)

| | |
|-----------------|--|
| End point title | Primary: Frequency of Subjects With a Deterioration of Hearing Threshold at Day 203 (Air Conduction) ^{[5][6]} |
|-----------------|--|

End point description:

Valid for Safety Analysis Set was used. Air conduction: The atmospheric transmission of sound to the inner ear through the external auditory canal and via structures of the middle ear. The ability of hearing is measured in decibel (dB). The hearing threshold, is the lowest sound pressure where the subject can still perceive a sound. The endpoint deterioration of hearing threshold ≥ 15 dB in two contiguous test frequencies means that hearing worsens ≥ 15 dB in two neighboring sound frequencies.

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

End point timeframe:

Day 168 (TV7) up to Day 203 (FUV8) of cycle 3

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Deterioration of hearing threshold at FUV8 (Day 203) is only evaluable for subjects that participated in 3 treatment cycles. For subjects that participated in 1 or 2 treatment cycles, the study had already ended after FUV3 (Day 84) or FUV6 (Day 168). Therefore no statistical analysis is possible.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Deterioration of hearing threshold at FUV8 (Day 203) is only evaluable for subjects that participated in 3 treatment cycles. For subjects that participated in 1 or 2 treatment cycles, the study had already ended after FUV3 (Day 84) or FUV6 (Day 168). Therefore no statistical analysis is possible.

| | | | | |
|---------------------------------|-----------------|--|--|--|
| End point values | 3 Cycles AM-101 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 70 | | | |
| Units: Number subjects affected | 3 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary: Frequency of Subjects With a Deterioration of Hearing Threshold at Day 84 (Air Conduction)

| | |
|------------------------|--|
| End point title | Secondary: Frequency of Subjects With a Deterioration of Hearing Threshold at Day 84 (Air Conduction) |
| End point description: | Valid for Safety Analysis Set was used. Air conduction: The atmospheric transmission of sound to the inner ear through the external auditory canal and via structures of the middle ear. The ability of hearing is measured in decibel (dB). The hearing threshold, is the lowest sound pressure where the subject can still perceive a sound. The endpoint deterioration of hearing threshold ≥ 15 dB in two contiguous test frequencies means that hearing worsens ≥ 15 dB in two neighboring sound frequencies. |
| End point type | Secondary |
| End point timeframe: | Day 1 (TV1) to Day 84 (FUV3) of cycle 1 |

| | | | | |
|---------------------------------|-----------------|-----------------|-----------------|--|
| End point values | 1 Cycle AM-101 | 2 Cycles AM-101 | 3 Cycles AM-101 | |
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 313 | 66 | 72 | |
| Units: Number subjects affected | 29 | 6 | 6 | |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | Subjects participating in 1 Cycle vs. 2 Cycles |
| Statistical analysis description: | Fisher's exact test to assess if there is a difference in deterioration of hearing threshold between subjects that had only 1 treatment cycle or those that decided later to have 2 treatment cycles. The analysis is based on the deterioration of hearing detected at FUV3 for all subjects in those groups. |
| Comparison groups | 1 Cycle AM-101 v 2 Cycles AM-101 |

| | |
|---|---------------|
| Number of subjects included in analysis | 379 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 1 |
| Method | Fisher exact |

| | |
|-----------------------------------|--|
| Statistical analysis title | Subjects participating in 1 Cycle vs. 3 Cycles |
|-----------------------------------|--|

Statistical analysis description:

Fisher's exact test to assess if there is a difference in deterioration of hearing threshold between subjects that had only 1 treatment cycle or those that decided later to have 3 treatment cycles. The analysis is based on the deterioration of hearing detected at FUV3 for all subjects in those groups.

| | |
|---|----------------------------------|
| Comparison groups | 1 Cycle AM-101 v 3 Cycles AM-101 |
| Number of subjects included in analysis | 385 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 1 |
| Method | Fisher exact |

| | |
|-----------------------------------|---|
| Statistical analysis title | Subjects participating in 2 Cycles vs. 3 Cycles |
|-----------------------------------|---|

Statistical analysis description:

Fisher's exact test to assess if there is a difference in deterioration of hearing threshold between subjects that decided to participate in 2 treatment cycle or those that decided later to have 3 treatment cycles. The analysis is based on the deterioration of hearing detected at FUV3 for all subjects in those groups.

| | |
|---|-----------------------------------|
| Comparison groups | 2 Cycles AM-101 v 3 Cycles AM-101 |
| Number of subjects included in analysis | 138 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 1 |
| Method | Fisher exact |

Secondary: Secondary: Frequency of Subjects With a Deterioration of Hearing Threshold at Day 168 (Air Conduction)

| | |
|-----------------|---|
| End point title | Secondary: Frequency of Subjects With a Deterioration of Hearing Threshold at Day 168 (Air Conduction) ^[7] |
|-----------------|---|

End point description:

Valid for Safety Analysis Set was used. Air conduction: The atmospheric transmission of sound to the inner ear through the external auditory canal and via structures of the middle ear. The ability of hearing is measured in decibel (dB). The hearing threshold, is the lowest sound pressure where the subject can still perceive a sound. The endpoint deterioration of hearing threshold ≥ 15 dB in two contiguous test frequencies means that hearing worsens ≥ 15 dB in two neighboring sound frequencies.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 84 (TV4) to Day 168 (FUV6) of cycle 2

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Deterioration of hearing threshold at FUV5 (Day 168) is only evaluable for subjects that participated in 2 or 3 treatment cycles. For subjects that participated only in one treatment cycle, the study had already ended after FUV3 (Day 84). Therefore, only one statistical comparison between subjects that participated in 2 vs. 3 treatment cycles, is possible.

| End point values | 2 Cycles AM-101 | 3 Cycles AM-101 | | |
|---------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 62 | 72 | | |
| Units: Number subjects affected | 4 | 6 | | |

Statistical analyses

| Statistical analysis title | Subjects participating in 2 Cycles vs. 3 Cycles |
|----------------------------|---|
|----------------------------|---|

Statistical analysis description:

Fisher's exact test to assess if there is a difference in deterioration of hearing threshold between subjects that decided to participate in 2 treatment cycle or those that decided later to have 3 treatment cycles. The analysis is based on the deterioration of hearing detected at FUV6 for all subjects in those groups.

| | |
|---|-----------------------------------|
| Comparison groups | 2 Cycles AM-101 v 3 Cycles AM-101 |
| Number of subjects included in analysis | 134 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7517 |
| Method | Fisher exact |

Secondary: Secondary: Frequency of Subjects With a Deterioration of Hearing Threshold at Day 252 (Air Conduction)

| | |
|-----------------|---|
| End point title | Secondary: Frequency of Subjects With a Deterioration of Hearing Threshold at Day 252 (Air Conduction) ^[8] |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 168 (TV7) to Day 252 (FUV9) of cycle 3

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Deterioration of hearing threshold at FUV9 (Day 252) is only evaluable for subjects that participated in 3 treatment cycles. For subjects that participated in 1 or 2 treatment cycles, the study had already ended after FUV3 (Day 84 or FUV6 (Day 168). Therefore, no statistical analysis is possible.

| | | | | |
|---------------------------------|-----------------|--|--|--|
| End point values | 3 Cycles AM-101 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 69 | | | |
| Units: Number subjects affected | 4 | | | |

Statistical analyses

No statistical analyses for this end point

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 | 19.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------------|
| Reporting group title | 1 Cycle AM-101 |
|-----------------------|----------------|

Reporting group description:

Subjects participated in 1 treatment cycle and received one round of 3 repeated doses of AM-101 gel (0.87 mg/mL) within 5 days (D0 - D4)

| | |
|-----------------------|-----------------|
| Reporting group title | 2 Cycles AM-101 |
|-----------------------|-----------------|

Reporting group description:

Subjects that participated in 2 treatment cycles of the AMPACT1 study, received 3 repeated doses of AM-101 gel (0.87 mg/mL) within 5 days (D0 - D4) in cycle 1 and after final follow-up (D84) of cycle 1, they rolled-over to treatment cycle 2 receiving once more 3 repeated doses of AM-101 gel (0.87 mg/mL) within 5 days (D84 - D88).

| | |
|-----------------------|-----------------|
| Reporting group title | 3 Cycles AM-101 |
|-----------------------|-----------------|

Reporting group description:

Subjects that participated in all 3 treatment cycles of the AMPACT1 study, received 3 x 3 repeated doses of AM-101 gel (0.87 mg/mL) within 5 days. The subjects could only roll-over if they completed the final follow-up of the previous cycle and were still eligible.

In cycle 1 treatment was within D0 - D4. Cycle 2 treatment within D84 - D88. And treatment for cycle 3 within D168-D172. Final follow-up after 3 treatment cycles was FUV9 (D252).

| Serious adverse events | 1 Cycle AM-101 | 2 Cycles AM-101 | 3 Cycles AM-101 |
|---|-----------------|-----------------|-----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 347 (0.86%) | 0 / 66 (0.00%) | 4 / 72 (5.56%) |
| 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) | | | |
| Cerebellopontine angle tumour | | | |
| subjects affected / exposed | 1 / 347 (0.29%) | 0 / 66 (0.00%) | 0 / 72 (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 |
| Cardiac disorders | | | |
| Atrioventricular block | | | |

| | | | |
|---|---|----------------|----------------|
| subjects affected / exposed | 1 / 347 (0.29%) | 0 / 66 (0.00%) | 0 / 72 (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 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 347 (0.00%) | 0 / 66 (0.00%) | 1 / 72 (1.39%) |
| 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 | | | |
| Lower motor neurone lesion | | | |
| subjects affected / exposed | 1 / 347 (0.29%) | 0 / 66 (0.00%) | 0 / 72 (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 |
| Migraine with aura | | | |
| subjects affected / exposed | 0 / 347 (0.00%) | 0 / 66 (0.00%) | 1 / 72 (1.39%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| | Additional description: Occurrence is causally related to procedure (intratympanic injection), Subject had it on both ears with bilateral tinnitus. | | |
| subjects affected / exposed | 0 / 347 (0.00%) | 0 / 66 (0.00%) | 1 / 72 (1.39%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 347 (0.00%) | 0 / 66 (0.00%) | 1 / 72 (1.39%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 3 %

| Non-serious adverse events | 1 Cycle AM-101 | 2 Cycles AM-101 | 3 Cycles AM-101 |
|---|--------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 157 / 347 (45.24%) | 36 / 66 (54.55%) | 57 / 72 (79.17%) |
| Vascular disorders | | | |

| | | | |
|--|-------------------------|------------------------|------------------------|
| Hypertension subjects affected / exposed occurrences (all) | 1 / 347 (0.29%) 1 | 2 / 66 (3.03%) 2 | 3 / 72 (4.17%) 3 |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 21 / 347 (6.05%) 21 | 4 / 66 (6.06%) 4 | 10 / 72 (13.89%) 10 |
| Ear and labyrinth disorders Ear discomfort subjects affected / exposed occurrences (all) | 26 / 347 (7.49%) 26 | 4 / 66 (6.06%) 4 | 5 / 72 (6.94%) 5 |
| Ear pain subjects affected / exposed occurrences (all) | 39 / 347 (11.24%) 39 | 12 / 66 (18.18%) 12 | 12 / 72 (16.67%) 12 |
| Eustachian tube obstruction subjects affected / exposed occurrences (all) | 1 / 347 (0.29%) 1 | 2 / 66 (3.03%) 2 | 0 / 72 (0.00%) 0 |
| Hypoacusis subjects affected / exposed occurrences (all) | 24 / 347 (6.92%) 24 | 8 / 66 (12.12%) 8 | 10 / 72 (13.89%) 10 |
| Tinnitus subjects affected / exposed occurrences (all) | 16 / 347 (4.61%) 16 | 3 / 66 (4.55%) 3 | 3 / 72 (4.17%) 3 |
| Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all) | 1 / 347 (0.29%) 1 | 2 / 66 (3.03%) 2 | 1 / 72 (1.39%) 1 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 2 / 347 (0.58%) 2 | 1 / 66 (1.52%) 1 | 5 / 72 (6.94%) 5 |
| Nasal obstruction subjects affected / exposed occurrences (all) | 0 / 347 (0.00%) 0 | 2 / 66 (3.03%) 2 | 1 / 72 (1.39%) 1 |
| Musculoskeletal and connective tissue disorders | | | |

Additional description: In non-serious adverse event section, under occurrences (all), reported numbers are "subjects affected".

| | | | |
|--|------------------------|----------------------|------------------------|
| Back pain subjects affected / exposed occurrences (all) | 2 / 347 (0.58%) 2 | 1 / 66 (1.52%) 1 | 4 / 72 (5.56%) 4 |
| Infections and infestations | | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 15 / 347 (4.32%) 15 | 8 / 66 (12.12%) 8 | 14 / 72 (19.44%) 14 |
| Otitis externa subjects affected / exposed occurrences (all) | 4 / 347 (1.15%) 4 | 3 / 66 (4.55%) 3 | 0 / 72 (0.00%) 0 |
| Otitis media subjects affected / exposed occurrences (all) | 5 / 347 (1.44%) 5 | 1 / 66 (1.52%) 1 | 3 / 72 (4.17%) 3 |
| Otitis media acute subjects affected / exposed occurrences (all) | 3 / 347 (0.86%) 3 | 1 / 66 (1.52%) 1 | 3 / 72 (4.17%) 3 |
| Pharyngitis subjects affected / exposed occurrences (all) | 1 / 347 (0.29%) 1 | 2 / 66 (3.03%) 2 | 7 / 72 (9.72%) 7 |
| Rhinitis subjects affected / exposed occurrences (all) | 3 / 347 (0.86%) 3 | 4 / 66 (6.06%) 4 | 2 / 72 (2.78%) 2 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|--|
| 23 October 2015 | <p>Main change: Cycle 2 and Cycle 3 were not offered any more.</p> <p>Rationale:</p> <p>Participation in the AMPACT2 trial has been offered to AM-101-CL-12-02 (TACTT3) participants as an option without any claims to efficacy beyond the 3 months acute stage, since the compound had never been tested before in patients with tinnitus older than 3 months.</p> <p>Preliminary data from the Stratum B interim analysis in the TACTT3 trial suggests that AM-101 may indeed still be active if initiated beyond the acute stage. However, therapeutic benefits seem to decrease the later treatment is initiated. In particular, the interim analysis of the changes in tinnitus loudness and TFI in Stratum B (tinnitus onset between 3 and 12 months prior) showed for the early post-acute stage higher levels of activity than at the later stage of the time window.</p> <p>In light of the data, which suggest only small therapeutic benefits, if any, from the initiation of treatment with AM-101 beyond 6 and especially beyond 9 months from onset, the Sponsor considers it appropriate to eliminate the optional Cycles 2 and 3 from the AMPACT2 trial. Even with the proposed modification, all TACTT3 participants will have the opportunity to receive for certain one full course / treatment cycle with the active study drug during AMPACT2.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported