



Clinical trial results:

Safety of AM-101 in Patients with Acute Inner Ear Tinnitus from Noise Trauma: a Dose-Finding Phase I/II Study

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2006-002692-41 |
| Trial protocol | DE |
| Global end of trial date | 15 March 2008 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 06 August 2016 |
| First version publication date | 06 August 2016 |

Trial information

Trial identification

| | |
|-----------------------|-----------------|
| Sponsor protocol code | AM-101-AAT-PHA1 |
|-----------------------|-----------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Laboratoires Auris SAS |
| Sponsor organisation address | CEEI Cap Alpha/ Avenue de l'Europe/ Clapiers, Montpellier Cedex 09, France, 34940 |
| Public contact | see below at Affiliate, see below at Affiliate, 0041 61 2011350, ear@aurismedical.com |
| Scientific contact | see below at Affiliate, see below at Affiliate, 0041 61 2011350, ear@aurismedical.com |
| Sponsor organisation name | Affiliate = Auris Medical AG |
| Sponsor organisation address | Falknerstr. 4, Basel, Switzerland, 4001 |
| Public contact | Thomas Meyer, Auris Medical AG, +41 61 201 13 50, ear@aurismedical.com |
| Scientific contact | Thomas Meyer, Auris Medical AG, +41 61 201 13 50, ear@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 | 07 August 2008 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 15 March 2008 |
| Global end of trial reached? | Yes |
| Global end of trial date | 15 March 2008 |
| 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 of the tolerability of the dose range expected to be needed for later clinical studies and to determine the nature of adverse reactions that could be expected.

The secondary objectives of the study were the preliminary evaluation of the potential therapeutic benefit of AM-101 in the treatment of inner ear tinnitus as well as the evaluation of systemic exposure following a single intratympanic injection of AM-101 (pharmacokinetics).

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), and the ethical principles outlined in the Declaration of Helsinki dated 1989, respectively in their most current version.

Background therapy:

N/A

Evidence for comparator:

N/A

| | |
|---|---------------|
| Actual start date of recruitment | 01 March 2007 |
| 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 | Germany: 24 |
| Worldwide total number of subjects | 24 |
| EEA total number of subjects | 24 |

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

Subject disposition

Recruitment

Recruitment details:

This study was designed as a double-blind, randomised, placebo-controlled, dose escalation, phase I/II study of a single intratympanic administration of AM-101 with a 2 month follow-up period. The study consisted of 4 dose cohorts (30, 90, 270 or 810 µg/ml) with 2 placebo and 4 verum patients per cohort. It involved 4 study sites in Germany.

Pre-assignment

Screening details:

Main inclusion criteria were: Age 18 - 60 years; permanent, stable, single tinnitus induced by acute acoustic trauma or sudden deafness; tinnitus on-set occurred within the past 3 months.

All screened patients had been randomised.

Period 1

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

Blinding implementation details:

The investigators as well as the subjects were blinded regarding the dose administered during the whole study. In particular, the gel formulation was of the same appearance for all doses and the placebo and revealed no differences during or following injection, neither to the investigator, nor to the patient.

Arms

| | |
|------------------------------|-----------------|
| Are arms mutually exclusive? | No |
| Arm title | AM-101 30 µg/ml |

Arm description:

Each patient received study treatment comprising a single intratympanic injection of 30 µg/ml of AM-101 followed by a 2 month treatment-free follow-up period.

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

0.25 ml of Esketamine HCl gel at a concentration of 30 µg/ml were injected.

| | |
|------------------|-----------------|
| Arm title | AM-101 90 µg/ml |
|------------------|-----------------|

Arm description:

Each patient received study treatment comprising a single intratympanic injection of 90 µg/ml of AM-101 followed by a 2 month treatment-free follow-up period.

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

0.25 ml of Esketamine HCl gel at a concentration of 90 µg/ml were injected.

| | |
|------------------|------------------|
| Arm title | AM-101 270 µg/ml |
|------------------|------------------|

Arm description:

Each patient received study treatment comprising a single intratympanic injection of 270 µg/ml of AM-101 followed by a 2 month treatment-free follow-up period.

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

0.25 ml of Esketamine HCl gel at a concentration of 270 µg/ml were injected.

| | |
|------------------|------------------|
| Arm title | AM-101 810 µg/ml |
|------------------|------------------|

Arm description:

Each patient received study treatment comprising a single intratympanic injection of 810 µg/ml of AM-101 followed by a 2 month treatment-free follow-up period.

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

0.25 ml of Esketamine HCl gel at a concentration of 810 µg/ml were injected.

| | |
|------------------|-------------------|
| Arm title | AM-101 pooled set |
|------------------|-------------------|

Arm description:

This is a pooled set of all 4 treatment cohorts receiving AM-101 which was used for the primary analysis.

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

0.25 ml of Esketamine HCl gel at a concentration of either 30, 90, 270 or 810 µg/ml were injected.

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

Arm description:

Matching placebo was administered following the same way (see above) with 2 subjects receiving placebo per dose cohort.

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

0.25 mL of Placebo (not containing Esketamine HCl) were injected.

| Number of subjects in period 1 | AM-101 30 µg/ml | AM-101 90 µg/ml | AM-101 270 µg/ml |
|---------------------------------------|-----------------|-----------------|------------------|
| Started | 4 | 4 | 4 |
| Completed | 4 | 4 | 3 |
| Not completed | 0 | 0 | 1 |
| Consent withdrawn by subject | - | - | 1 |

| Number of subjects in period 1 | AM-101 810 µg/ml | AM-101 pooled set | Placebo |
|---------------------------------------|------------------|-------------------|---------|
| Started | 4 | 16 | 8 |
| Completed | 4 | 15 | 8 |
| Not completed | 0 | 1 | 0 |
| Consent withdrawn by subject | - | 1 | - |

Baseline characteristics

Reporting groups

| | |
|---|-------------------|
| Reporting group title | AM-101 30 µg/ml |
| Reporting group description: | |
| Each patient received study treatment comprising a single intratympanic injection of 30 µg/ml of AM-101 followed by a 2 month treatment-free follow-up period. | |
| Reporting group title | AM-101 90 µg/ml |
| Reporting group description: | |
| Each patient received study treatment comprising a single intratympanic injection of 90 µg/ml of AM-101 followed by a 2 month treatment-free follow-up period. | |
| Reporting group title | AM-101 270 µg/ml |
| Reporting group description: | |
| Each patient received study treatment comprising a single intratympanic injection of 270 µg/ml of AM-101 followed by a 2 month treatment-free follow-up period. | |
| Reporting group title | AM-101 810 µg/ml |
| Reporting group description: | |
| Each patient received study treatment comprising a single intratympanic injection of 810 µg/ml of AM-101 followed by a 2 month treatment-free follow-up period. | |
| Reporting group title | AM-101 pooled set |
| Reporting group description: | |
| This is a pooled set of all 4 treatment cohorts receiving AM-101 which was used for the primary analysis. | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Matching placebo was administered following the same way (see above) with 2 subjects receiving placebo per dose cohort. | |

| Reporting group values | AM-101 30 µg/ml | AM-101 90 µg/ml | AM-101 270 µg/ml |
|--|-----------------|-----------------|------------------|
| Number of subjects | 4 | 4 | 4 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 4 | 4 | 4 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 20 | 25.8 | 26.5 |
| standard deviation | ± 1.4 | ± 5.5 | ± 8.8 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 0 | 0 | 1 |
| Male | 4 | 4 | 3 |

| Reporting group values | AM-101 810 µg/ml | AM-101 pooled set | Placebo |
|---|------------------|-------------------|---------|
| Number of subjects | 4 | 16 | 8 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 4 | 16 | 8 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous Units: years | | | |
| arithmetic mean | 28.5 | 25.2 | 33 |
| standard deviation | ± 11.1 | ± 7.6 | ± 17.3 |
| Gender categorical Units: Subjects | | | |
| Female | 1 | 2 | 1 |
| Male | 3 | 14 | 7 |

| Reporting group values | Total | | |
|---|-------|--|--|
| Number of subjects | 24 | | |
| Age categorical Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 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) | 24 | | |
| From 65-84 years | 0 | | |
| 85 years and over | 0 | | |
| Age continuous Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical Units: Subjects | | | |
| Female | 3 | | |
| Male | 21 | | |

End points

End points reporting groups

| | |
|---|-------------------|
| Reporting group title | AM-101 30 µg/ml |
| Reporting group description: Each patient received study treatment comprising a single intratympanic injection of 30 µg/ml of AM-101 followed by a 2 month treatment-free follow-up period. | |
| Reporting group title | AM-101 90 µg/ml |
| Reporting group description: Each patient received study treatment comprising a single intratympanic injection of 90 µg/ml of AM-101 followed by a 2 month treatment-free follow-up period. | |
| Reporting group title | AM-101 270 µg/ml |
| Reporting group description: Each patient received study treatment comprising a single intratympanic injection of 270 µg/ml of AM-101 followed by a 2 month treatment-free follow-up period. | |
| Reporting group title | AM-101 810 µg/ml |
| Reporting group description: Each patient received study treatment comprising a single intratympanic injection of 810 µg/ml of AM-101 followed by a 2 month treatment-free follow-up period. | |
| Reporting group title | AM-101 pooled set |
| Reporting group description: This is a pooled set of all 4 treatment cohorts receiving AM-101 which was used for the primary analysis. | |
| Reporting group title | Placebo |
| Reporting group description: Matching placebo was administered following the same way (see above) with 2 subjects receiving placebo per dose cohort. | |

Primary: Safety: Incidence of hearing loss grade 2 at two contiguous test frequencies at day 30 compared to baseline by treatment

| | |
|--|---|
| End point title | Safety: Incidence of hearing loss grade 2 at two contiguous test frequencies at day 30 compared to baseline by treatment ^[1] |
| End point description: The primary variable for the safety assessment was the incidence of a hearing loss \geq Grade 2 (i.e. a loss of ≥ 25 dB) in any two contiguous kHz levels in the treated ear. The primary endpoint was on D30. Any hearing loss induced by the treatment and/or the procedure was hypothesised to become permanent by this time. As defined in the statistical analysis plan: The total number and percent of primary safety events has been summarised by treatment. No formal statistical tests have been used to compare group differences. The ITT analysis set was used for the primary data analyses and is identical with the safety set in this study. The key study results are presented in the pooled verum data sets as the the primary study outcome. | |
| End point type | Primary |
| End point timeframe: Baseline to D30 | |
| Notes: [1] - 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: No statistical analysis was performed. Number of events was zero. | |

| End point values | AM-101 30 µg/ml | AM-101 90 µg/ml | AM-101 270 µg/ml | AM-101 810 µg/ml |
|-----------------------------|--------------------|--------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4 | 4 | 3 | 4 |
| Units: number subjects | 0 | 0 | 0 | 0 |

| End point values | AM-101 pooled set | Placebo | | |
|-----------------------------|----------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 15 | 8 | | |
| Units: number subjects | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Efficacy: Changes in tinnitus severity as measured by the TBF-12

| | |
|-----------------|--|
| End point title | Efficacy: Changes in tinnitus severity as measured by the TBF-12 |
|-----------------|--|

End point description:

The primary variable for the efficacy assessment was the measure of tinnitus handicap with the TBF-12 score. The primary endpoint was the change in TBF-12 between D0 and D30.

| | |
|----------------------|---------|
| End point type | Primary |
| End point timeframe: | |
| Baseline to Day 30 | |

| End point values | AM-101 30 µg/ml | AM-101 90 µg/ml | AM-101 270 µg/ml | AM-101 810 µg/ml |
|--------------------------------------|--------------------|--------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4 | 4 | 3 | 4 |
| Units: TBF-12 score | | | | |
| arithmetic mean (standard deviation) | 0.5 (± 3.32) | 0.25 (± 5.3) | -1.67 (± 5.5) | 0.5 (± 2.7) |

| End point values | AM-101 pooled set | Placebo | | |
|--------------------------------------|----------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 15 | 8 | | |
| Units: TBF-12 score | | | | |
| arithmetic mean (standard deviation) | 0 (± 3.9) | -0.13 (± 3) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Change in TBF-12 score from Baseline to D30 |
| Comparison groups | Placebo v AM-101 pooled set |
| Number of subjects included in analysis | 23 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Mixed models analysis |
| Parameter estimate | Estimate |
| Point estimate | 0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.48 |
| upper limit | 7.68 |

Secondary: Efficacy: Improvement of the score of the tinnitus loudness question (TLQ)

| | |
|------------------------|--|
| End point title | Efficacy: Improvement of the score of the tinnitus loudness question (TLQ) |
| End point description: | The tinnitus loudness was documented by the patients via a 10 point visual analogue scale (VAS). |
| End point type | Secondary |
| End point timeframe: | Day 0 - Day 30 |

| | | | | |
|---------------------------------------|--------------------|--------------------|---------------------|---------------------|
| End point values | AM-101 30 µg/ml | AM-101 90 µg/ml | AM-101 270 µg/ml | AM-101 810 µg/ml |
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4 | 4 | 3 | 4 |
| Units: 10 point visual analogue scale | | | | |
| arithmetic mean (standard deviation) | -1 (± 1.15) | -1.5 (± 0.58) | -1.33 (± 0.58) | -0.5 (± 1) |

| | | | | |
|---------------------------------------|----------------------|-----------------|--|--|
| End point values | AM-101 pooled set | Placebo | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 15 | 8 | | |
| Units: 10 point visual analogue scale | | | | |

| | | | | |
|--------------------------------------|---------------------|---------------------|--|--|
| arithmetic mean (standard deviation) | -1.07 (\pm 0.88) | -0.31 (\pm 1.79) | | |
|--------------------------------------|---------------------|---------------------|--|--|

Statistical analyses

| | |
|--|---------------------------------------|
| Statistical analysis title | Difference Placebo vs. AM-101 overall |
| Statistical analysis description: D0 to D30 | |
| Comparison groups | Placebo v AM-101 pooled set |
| Number of subjects included in analysis | 23 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Mixed models analysis |
| Parameter estimate | Estimate |
| Point estimate | -0.56 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.92 |
| upper limit | 1.8 |

Secondary: Efficacy: Change in minimum masking level (MML)

| | |
|---|---|
| End point title | Efficacy: Change in minimum masking level (MML) |
| End point description: A further secondary efficacy endpoint was the change from baseline to D30 in the minimum tinnitus masking level (MML) measured by the investigators. The binaural MML was assessed with a narrow band of noise. | |
| End point type | Secondary |
| End point timeframe: Day 0 - Day 30 | |

| End point values | AM-101 30 μ g/ml | AM-101 90 μ g/ml | AM-101 270 μ g/ml | AM-101 810 μ g/ml |
|--------------------------------------|-------------------------|-------------------------|--------------------------|--------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4 | 4 | 3 | 4 |
| Units: dB | | | | |
| arithmetic mean (standard deviation) | -1 (\pm 6.48) | -2 (\pm 4) | 1 (\pm 3.61) | -6.25 (\pm 2.5) |

| | | | | |
|-------------------------|----------------------|---------|--|--|
| End point values | AM-101 pooled set | Placebo | | |
|-------------------------|----------------------|---------|--|--|

| | | | | |
|--------------------------------------|---------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 15 | 8 | | |
| Units: dB | | | | |
| arithmetic mean (standard deviation) | -2.29 (\pm 4.84) | -0.5 (\pm 1.87) | | |

Statistical analyses

| | |
|---|---------------------------------------|
| Statistical analysis title | Difference Placebo vs. AM-101 overall |
| Statistical analysis description: D0 - D30 | |
| Comparison groups | AM-101 pooled set v Placebo |
| Number of subjects included in analysis | 23 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Mixed models analysis |
| Parameter estimate | Estimate |
| Point estimate | 1.24 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.77 |
| upper limit | 9.26 |

Secondary: PK: Maximum plasma drug concentration level (Cmax) - Esketamine

| | |
|-----------------|--|
| End point title | PK: Maximum plasma drug concentration level (Cmax) - Esketamine ^[2] |
|-----------------|--|

End point description:

Plasma samples of the 2 highest dose cohorts (270 and 810 µg/ml) were analysed for PK. Concentrations above lower limit of quantification (LLOQ) could be detected in only 1 of the 4 patients in the 270 g/ml dose group, but in 4 out of 4 in the 810 g/ml group. Therefore the samples of 5 patients could be included in the pharmacokinetic (PK) analysis.

Statistics N/A - Standard PK analysis methods were used.

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

End point timeframe:

Sampling on the day of treatment D0, with samples being drawn prior to treatment administration and 15 min, 30 min, 45 min, 1 hour, 3 hours and 6 hours after treatment.

Notes:

[2] - 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: For the PK analysis only patients from the 2 high dose cohorts were included.

| | | | | |
|--------------------------------------|--------------------|--|--|--|
| End point values | AM-101 pooled set | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 5 ^[3] | | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | 0.23 (\pm 0.06) | | | |

Notes:

[3] - See description in Cmax - Esketamine

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Time to maximum plasma concentration (Tmax) - Esketamine

| | |
|-----------------|---|
| End point title | PK: Time to maximum plasma concentration (Tmax) - Esketamine ^[4] |
|-----------------|---|

End point description:

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

End point timeframe:

see Cmax - Esketamine

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: For the PK analysis only patients from the 2 high dose cohorts were included.

| End point values | AM-101 pooled set | | | |
|--------------------------------------|-------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 5 ^[5] | | | |
| Units: hours | | | | |
| arithmetic mean (standard deviation) | 0.56 (± 0.31) | | | |

Notes:

[5] - See description in Cmax - Esketamine

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Area under the plasma concentration-time curve (AUC 0-6) - Esketamine

| | |
|-----------------|--|
| End point title | PK: Area under the plasma concentration-time curve (AUC 0-6) - Esketamine ^[6] |
|-----------------|--|

End point description:

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

End point timeframe:

see Cmax

Notes:

[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: For the PK analysis only patients from the 2 high dose cohorts were included.

| | | | | |
|--------------------------------------|-------------------|--|--|--|
| End point values | AM-101 pooled set | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 5 ^[7] | | | |
| Units: ng*h/mL | | | | |
| arithmetic mean (standard deviation) | 0.66 (± 0.12) | | | |

Notes:

[7] - See description in Cmax - Esketamine

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Maximum plasma drug concentration level (Cmax) - S-Norketamine

| | |
|-----------------|---|
| End point title | PK: Maximum plasma drug concentration level (Cmax) - S-Norketamine ^[8] |
|-----------------|---|

End point description:

see Cmax - Esketamine

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

End point timeframe:

Sampling on the day of treatment D0, with samples being drawn prior to treatment administration and 15 min, 30 min, 45 min, 1 hour, 3 hours and 6 hours after treatment.

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: For the PK analysis only patients from the 2 high dose cohorts were included.

| | | | | |
|--------------------------------------|-------------------|--|--|--|
| End point values | AM-101 pooled set | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 5 ^[9] | | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | 0.15 (± 0.02) | | | |

Notes:

[9] - See description in Cmax - Esketamine

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Time to maximum plasma concentration (Tmax) - S-Norketamine

| | |
|-----------------|---|
| End point title | PK: Time to maximum plasma concentration (Tmax) - S-Norketamine ^[10] |
|-----------------|---|

End point description:

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

End point timeframe:

see Cmax - Esketamine

Notes:

[10] - 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: For the PK analysis only patients from the 2 high dose cohorts were included.

| | | | | |
|--------------------------------------|-------------------|--|--|--|
| End point values | AM-101 pooled set | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 5 ^[11] | | | |
| Units: hours | | | | |
| arithmetic mean (standard deviation) | 2.5 (± 1) | | | |

Notes:

[11] - See description in Cmax - Esketamine

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Area under the plasma concentration-time curve (AUC 0-6) - S-Norketamine

| | |
|-----------------|--|
| End point title | PK: Area under the plasma concentration-time curve (AUC 0-6) - S-Norketamine ^[12] |
|-----------------|--|

End point description:

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

End point timeframe:

see Cmax - Esketamine

Notes:

[12] - 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: For the PK analysis only patients from the 2 high dose cohorts were included.

| | | | | |
|--------------------------------------|-------------------|--|--|--|
| End point values | AM-101 pooled set | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 5 ^[13] | | | |
| Units: ng*h/mL | | | | |
| arithmetic mean (standard deviation) | 0.73 (± 0.16) | | | |

Notes:

[13] - See description in Cmax - Esketamine

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

After single-dose treatment, study subjects were followed for 60 days with 3 follow-up visits at D7, D30 and D60. At each visit, AEs were recorded.

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

Dictionary used

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

| | |
|--------------------|-----|
| Dictionary version | 9.1 |
|--------------------|-----|

Reporting groups

| | |
|-----------------------|-----------------|
| Reporting group title | AM-101 30 µg/ml |
|-----------------------|-----------------|

| | |
|------------------------------|---|
| Reporting group description: | - |
|------------------------------|---|

| | |
|-----------------------|-----------------|
| Reporting group title | AM-101 90 µg/ml |
|-----------------------|-----------------|

| | |
|------------------------------|---|
| Reporting group description: | - |
|------------------------------|---|

| | |
|-----------------------|------------------|
| Reporting group title | AM-101 270 µg/ml |
|-----------------------|------------------|

| | |
|------------------------------|---|
| Reporting group description: | - |
|------------------------------|---|

| | |
|-----------------------|------------------|
| Reporting group title | AM-101 810 µg/ml |
|-----------------------|------------------|

| | |
|------------------------------|---|
| Reporting group description: | - |
|------------------------------|---|

| | |
|-----------------------|-------------------|
| Reporting group title | AM-101 pooled set |
|-----------------------|-------------------|

| | |
|------------------------------|---|
| Reporting group description: | - |
|------------------------------|---|

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

| | |
|------------------------------|---|
| Reporting group description: | - |
|------------------------------|---|

| Serious adverse events | AM-101 30 µg/ml | AM-101 90 µg/ml | AM-101 270 µg/ml |
|---|-----------------|-----------------|------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

| Serious adverse events | AM-101 810 µg/ml | AM-101 pooled set | Placebo |
|---|------------------|-------------------|---------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 16 (0.00%) | 0 / 8 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | AM-101 30 µg/ml | AM-101 90 µg/ml | AM-101 270 µg/ml |
|---|-----------------|-----------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | 2 / 4 (50.00%) | 4 / 4 (100.00%) |
| Investigations | | | |
| Paracentesis ear abnormal | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 2 / 4 (50.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 2 | 1 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Headache | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Neuromuscular blockade | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Paresthesia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 4 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Ear and labyrinth disorders | | | |
| Deafness | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Deafness unilateral | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Ear pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Middle ear inflammation | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tinnitus | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vertigo | | | |

| | | | |
|--|---------------------|--------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 1 / 4 (25.00%) 1 | 0 / 4 (0.00%) 0 | 1 / 4 (25.00%) 1 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 | 1 / 4 (25.00%) 1 |

| Non-serious adverse events | AM-101 810 µg/ml | AM-101 pooled set | Placebo |
|---|--------------------|----------------------|---------------------|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 3 / 4 (75.00%) | 11 / 16 (68.75%) | 6 / 8 (75.00%) |
| Investigations Paracentesis ear abnormal subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 3 / 16 (18.75%) 3 | 0 / 8 (0.00%) 0 |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 0 / 16 (0.00%) 0 | 2 / 8 (25.00%) 2 |
| Headache subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 2 / 16 (12.50%) 2 | 1 / 8 (12.50%) 1 |
| Neuromuscular blockade subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 2 / 16 (12.50%) 2 | 0 / 8 (0.00%) 0 |
| Paresthesia subjects affected / exposed occurrences (all) | 0 / 4 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 8 (0.00%) 0 |
| Ear and labyrinth disorders Deafness | | | |

| | | | |
|-----------------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 4 (25.00%) | 1 / 16 (6.25%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Deafness unilateral | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 16 (6.25%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Ear pain | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 1 / 16 (6.25%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Middle ear inflammation | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 16 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Tinnitus | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 1 / 16 (6.25%) | 1 / 8 (12.50%) |
| occurrences (all) | 2 | 2 | 1 |
| Vertigo | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 1 / 16 (6.25%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 16 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | 4 / 16 (25.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 2 | 4 | 1 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 16 (6.25%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 1 | 1 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 10 May 2007 | The aim of this amendment was to include an evaluation of the potential systemic exposure following a single intratympanic injection of AM-101. The pharmacokinetic characteristics of Esketamine in plasma were to be characterised at the two higher doses tested (270 µg/mL and 810 µg/mL), including determination of the parent and the principal metabolite (S)-Norketamine. |
| 07 June 2007 | - Patients with severe or disabling permanent inner ear tinnitus which set in with sudden deafness were included. |
| 17 September 2007 | - An interim analysis at the end of the 270 µg/mL dose cohort (after Day 7 of the last patient included in this cohort) was added. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported