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 screeened. After 2 screening failurs, 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 (± 2.709)	38.44 (± 2.753)	36.63 (± 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: Occurence of clinically relevant hearing deterioration

End point title	Safety: Occurence of clinically relevant hearing deterioration

End point description:

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

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