Clinical trial results:
Multicenter randomized controlled phase 2 trial to evaluate AM-125 in the treatment of acute peripheral vertigo following neurosurgery (TRAVERS)

Summary

EudraCT number	2018-002474-52
Trial protocol	BE CZ PL DE GB SK IT
Global end of trial date	28 March 2022

Results information

Result version number	v1 (current)
This version publication date	30 August 2023
First version publication date	30 August 2023

Trial information

Trial identification

Sponsor protocol code	AM-125-CL-18-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03908567
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Auris Medical AG
Sponsor organisation address	Peter Merian Street 90, Basel, Switzerland,
Public contact	CEO, Auris Medical AG, tm@aurismedical.com
Scientific contact	CEO, Auris Medical AG, tm@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	29 August 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 March 2022
Global end of trial reached?	Yes
Global end of trial date	28 March 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The study consisted of two parts (Part A and B):
Primary objective of Part A was
a. to explore and provide an estimate of the dose response curve for AM-125, and
b. to evaluate the efficacy of AM-125 compared to placebo in reducing the symptoms of vestibular dysfunction and accelerating vestibular compensation following surgery-induced acute vestibular syndrome (AVS).
Part A contained as well an oral open-label arm with 16 mg betahistine dihydrochloride tablets (authorized in the EU).

The primary objective of Part B was to evaluate the efficacy of two selected doses of AM-125 versus placebo, as determined based on the results from Part A, in reducing the symptoms of vestibular dysfunction and accelerating vestibular compensation following surgery-induced acute vestibular syndrome compared to placebo.
The 10 and 20 mg cohorts were selected for efficacy testing in Part B.

All subjects performed twice daily a home-based vestibular rehabilitation therapy exercise program.

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: -

Evidence for comparator: -

Actual start date of recruitment	18 July 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 7
Country: Number of subjects enrolled	Slovakia: 22
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Czechia: 51
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 21
Country: Number of subjects enrolled	Italy: 15
Worldwide total number of subjects	124
EEA total number of subjects	124

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)	109
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study consisted of a Screening phase which started 28 days prior to Day 0 when the patient underwent surgery. Patients were randomized to treatment on Day 3. The treatment phase continued up to Day 31 with three Follow up visits (FUVs): Day 7 (FUV1), Day 14 (FUV2), and Day 31 (FUV3). Final follow-up phase continued until Day 45 (FUV4).

Pre-assignment

Screening details:

The study consisted of two parts: In part A, a total of 67 subjects were screened at approximately 20 sites in Europe and Australia, of which 49 were randomized to AM-125 or placebo and 16 to oral betahistine (open label). In part B, a total of 102 subjects were screened of which 75 subjects were randomized at the same sites.

Period 1

Period 1 title	Treatment and follow-up (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

There were no differences in the spray pump devices (active vs. placebo) and no discernible difference in the odor or appearance of the spray formulations.
The oral arm was an open-label arm for reference.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Recruitment into this arm took place in part A (n=7) and part B (n=25).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray, solution
Routes of administration	Intranasal use

Dosage and administration details:

1 actuation in each nostril. Three times daily for 28 days. 100 uL per actuation (0 mg/ml betahistine dihydrochloride).

Arm title	Intranasal AM-125, 1 mg

Arm description:

Recruitment into this arm happenend solely in part A.

Arm type	Experimental
Investigational medicinal product name	AM-125
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray, solution
Routes of administration	Intranasal use

Dosage and administration details:

1 actuation in each nostril. Three times daily for 28 days. 100 uL per actuation (5 mg/ml betahistine dihydrochloride).

Arm title	Intranasal AM-125, 10 mg

Arm description:	
Recruitment into this arm took place in part A (n=9) and part B (n=25).	
Arm type	Experimental
Investigational medicinal product name	AM-125
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray, solution
Routes of administration	Intranasal use
Dosage and administration details:	
1 actuation in each nostril. Three times daily for 28 days. 100 uL per actuation (50 mg/ml betahistine dihydrochloride).	
Arm title	Intranasal AM-125, 20 mg
Arm description:	
Recruitment into this arm took place in part A (n=8) and part B (n=25).	
Arm type	Experimental
Investigational medicinal product name	AM-125
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray, solution
Routes of administration	Intranasal use
Dosage and administration details:	
1 actuation in each nostril. Three times daily for 28 days. 100 uL per actuation (100 mg/ml betahistine dihydrochloride).	
Arm title	Oral betahistine
Arm description:	
Was added for reference without placebo. Open-label arm.	
Arm type	Active comparator
Investigational medicinal product name	Oral betahistine, 16 mg tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use
Dosage and administration details:	
Three times daily a tablet containing 16 mg betahistine dihydrochloride for 28 days (tablet approved and holding a marketing authorization in the EU).	

Number of subjects in period 1	Placebo	Intranasal AM-125, 1 mg	Intranasal AM-125, 10 mg
Started	32	9	34
Completed	31	8	32
Not completed	1	1	2
Consent withdrawn by subject	-	-	2
Adverse event, non-fatal	-	1	-
Adverse event related to surgery, but not IMP	-	-	-
Lost to follow-up	1	-	-

Number of subjects in period 1	Intranasal AM-125, 20 mg	Oral betahistine

Started	33	16
Completed	29	14
Not completed	4	2
Consent withdrawn by subject	-	1
Adverse event, non-fatal	2	-
Adverse event related to surgery, but not IMP	2	1
Lost to follow-up	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Recruitment into this arm took place in part A (n=7) and part B (n=25).	
Reporting group title	Intranasal AM-125, 1 mg
Reporting group description:	
Recruitment into this arm happenend solely in part A.	
Reporting group title	Intranasal AM-125, 10 mg
Reporting group description:	
Recruitment into this arm took place in part A (n=9) and part B (n=25).	
Reporting group title	Intranasal AM-125, 20 mg
Reporting group description:	
Recruitment into this arm took place in part A (n=8) and part B (n=25).	
Reporting group title	Oral betahistine
Reporting group description:	
Was added for reference without placebo. Open-label arm.	

Reporting group values	Placebo	Intranasal AM-125, 1 mg	Intranasal AM-125, 10 mg
Number of subjects	32	9	34
Age categorical			
Randomization was stratified by age at baseline (< 50 years of age, ≥ 50 years of age).			
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)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Adults > 50 years	20	4	20
Adults < 50 years	12	5	14
Age continuous			
Units: years			
arithmetic mean	59.2	58.5	59.2
standard deviation	± 5.13	± 7.23	± 6.82
Gender categorical			
Units: Subjects			
Female	22	5	18
Male	10	4	16

Reporting group values	Intranasal AM-125, 20 mg	Oral betahistine	Total
Number of subjects	33	16	124

Age categorical			
Randomization was stratified by age at baseline (< 50 years of age, ≥ 50 years of age).			
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)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Adults > 50 years	22	12	78
Adults < 50 years	11	4	46
Age continuous			
Units: years			
arithmetic mean	58.8	58.0	
standard deviation	± 5.4	± 6.15	-
Gender categorical			
Units: Subjects			
Female	14	11	70
Male	19	5	54

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Recruitment into this arm took place in part A (n=7) and part B (n=25).	
Reporting group title	Intranasal AM-125, 1 mg
Reporting group description:	
Recruitment into this arm happenend solely in part A.	
Reporting group title	Intranasal AM-125, 10 mg
Reporting group description:	
Recruitment into this arm took place in part A (n=9) and part B (n=25).	
Reporting group title	Intranasal AM-125, 20 mg
Reporting group description:	
Recruitment into this arm took place in part A (n=8) and part B (n=25).	
Reporting group title	Oral betahistine
Reporting group description:	
Was added for reference without placebo. Open-label arm.	
Subject analysis set title	Enrolled Set
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects who signed informed consent.	
Subject analysis set title	Intention to Treat Set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Includes all randomized subjects. Subjects are analyzed according to their randomized treatment.	
Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Includes all subjects who received randomized therapy. Subjects are summarized according to the treatment received.	
Subject analysis set title	Per Protocol Set
Subject analysis set type	Per protocol
Subject analysis set description:	
Includes all subjects from the ITT Analysis Set who received at least one dose of study drug and are without major protocol deviations which would interfere with the analysis of the primary endpoint. Subjects are analyzed according to the treatment received.	

Primary: Improvement in tandem Romberg test (eyes closed)

End point title	Improvement in tandem Romberg test (eyes closed)[1]
End point description:	
Tandem Romberg Test is a physical assessment used to evaluate disturbance in subject's balance. In the present protocol, subjects were asked to stand straight in tandem stand (the heel of one foot touching the toes of the other foot, shoes removed) with eyes closed. The time for which the subjects were able to hold this position until they either opened their eyes or moved their feet in order to maintain balance for a maximum of 30 seconds, was measured by the examiner. On each occasion the assessment was performed three times. The best performance was used for efficacy analysis. The assessment was performed at SV, TV and at all FUVs.	
End point type	Primary
End point timeframe:	
From TV (baseline) to FUV4.	

Notes:

[1] - 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: In this entry major endpoints are presented. The final analysis did focus on the 10 mg and 20 mg cohorts. Therefore, the statistic for the 1 mg cohort is not presented here. For more information the reader can refer to the publication of the study or send a request to the sponsor.

End point values	Placebo	Intranasal AM-125, 10 mg	Intranasal AM-125, 20 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	32	31	
Units: seconds				
least squares mean (standard error)	10.7 (± 1.38)	10.5 (± 1.35)	11.2 (± 1.37)	

Statistical analyses

Statistical analysis title	Improvement in TRT between Placebo and AM-125

Statistical analysis description:

In the MMRM model, the dependent variable was the endpoint change in the tandem Romberg test from baseline to FUV4. Randomized treatment, time (i.e. FUV1, 2, 3 and 4) and time by-randomized treatment interaction were fitted as fixed effects with baseline value as a covariate. Subject were included as a random effect. Analysis was stratified by age. The primary estimand of interest was the contrast between AM-125 doses and placebo at FUV4.

Comparison groups	Placebo v Intranasal AM-125, 10 mg v Intranasal AM-125, 20 mg
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.8 [2]
Method	Mixed models analysis

Notes:

[2] - AM-125 10 mg vs. Placebo p-value = 0.9
AM-125 20 mg vs. Placebo p-value = 0.8

Secondary: Improvement in time standing on foam (SOF)

End point title	Improvement in time standing on foam (SOF)[3]

End point description:

Subjects were asked to stand straight on a foam plate with parallel feet (shoes removed) and eyes closed. An examiner measured the time that subjects were able to hold this position until they either open their eyes or move their feet in order to maintain balance for a maximum of 30 seconds.

End point type	Secondary

End point timeframe:

From baseline to FUV2.

Notes:

[3] - 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: In this entry major endpoints are presented. The final analysis did focus on the 10 mg and 20 mg cohorts. Therefore, the statistic for the 1 mg cohort is not presented here. For more information the reader can refer to the publication of the study or send a request to the sponsor.

End point values	Placebo	Intranasal AM-125, 10 mg	Intranasal AM-125, 20 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	32	31	
Units: seconds				
least squares mean (standard error)	14.77 (± 1.83)	15.89 (± 1.78)	18.46 (± 1.85)	

Statistical analyses

Statistical analysis title	Improvement in SOF between Placebo and AM-125

Statistical analysis description:

Same model as for primary endpoint was used.

Comparison groups	Placebo v Intranasal AM-125, 10 mg v Intranasal AM-125, 20 mg
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.158 [4]
Method	Mixed models analysis

Notes:

[4] - AM-125 10 mg vs. Placebo p-value = 0.66
AM-125 20 mg vs. Placebo p-value = 0.16

Other pre-specified: Change in the Vestibular Rehabilitation Benefit Questionnaire score from

End point title	Change in the Vestibular Rehabilitation Benefit Questionnaire score from[5]

End point description:

Subjects were self-assessing their vestibular symptoms and the impact of vestibular dysfunction with the Vestibular Rehabilitation Benefit Questionnaire (Morris et al. 2009) at all visits.
The VRBQ as a measure of vestibular deficit was analyzed only in Part B of the study. The score decreased over time in all treatment groups with the largest improvements observed in the AM 125 20 mg group.
The improvements (LS Mean change), using MMRM analysis, compared to baseline in VRBQ score did not reach statistical significance for either treatment group when compared to placebo. The trend for better improvement in the AM-125 20 mg group was driven primarily by reduction in subjective dizziness and anxiety among symptoms and lower impact on quality of life.
The results presented below correspond to the FUV3.

End point type	Other pre-specified

End point timeframe:

From TV (baseline) to FUV3

Notes:

[5] - 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: In this entry major endpoints are presented. The final analysis did focus on the 10 mg and 20 mg cohorts. Therefore, the statistic for the 1 mg cohort is not presented here. For more information the reader can refer to the publication of the study or send a request to the sponsor.

End point values	Placebo	Intranasal AM-125, 10 mg	Intranasal AM-125, 20 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	34	33	
Units: Score				
least squares mean (standard error)	-27.5 (± 2.9)	-22.65 (± 2.9)	-28.76 (± 3.1)	

Statistical analyses

Statistical analysis title	Improvement in VRBQ between Placebo and AM-125

Statistical analysis description:

Results are provided for FUV3

Comparison groups	Placebo v Intranasal AM-125, 10 mg v Intranasal AM-125, 20 mg
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.24 [6]
Method	Mixed models analysis

Notes:

[6] - AM-125 10 mg vs. Placebo p-value = 0.24
AM-125 20 mg vs. Placebo p-value = 0.78

Post-hoc: Resolution of Spontaneous Nystagmus

End point title	Resolution of Spontaneous Nystagmus[7]

End point description:

Nystagmus is a condition of involuntary eye movement and is commonly seen in many types of balance disorder.
The number of subjects with presence of nystagmus and without nystagmus were analyzed at all the FUV visits in treatment groups of AM 125 10 mg, AM 125 20 mg, and placebo. The most significant results were observed at FUV4, which are reported hereby.

End point type	Post-hoc

End point timeframe:

From TV (baseline) to FUV4

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: In this entry major endpoints are presented. The final analysis did focus on the 10 mg and 20 mg cohorts. Therefore, the statistic for the 1 mg cohort is not presented here. For more information the reader can refer to the publication of the study.

End point values	Placebo	Intranasal AM-125, 10 mg	Intranasal AM-125, 20 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	34	33	
Units: number	8	10	14	

Statistical analyses

Statistical analysis title	Resolution of spontaneous nystagmus
Comparison groups	Placebo v Intranasal AM-125, 10 mg v Intranasal AM-125, 20 mg
Number of subjects included in analysis	99
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.47 [8]
Method	Mixed models analysis

Notes:

[8] - AM-125 10 mg vs. Placebo p-value = 0.27
AM-125 20 mg vs. Placebo p-value = 0.47

Post-hoc: Change in Tandem Romberg test excluding subjects with substantial vestibular compensation at baseline

End point title	Change in Tandem Romberg test excluding subjects with substantial vestibular compensation at baseline[9]

End point description:

Mapping the change in the Tandem Romberg test against the change in the Standing on Foam test at a subject level revealed several cases that were unable to perform the Tandem Romberg test at baseline, but achieved meaningful or even maximum Standing on Foam scores. This pointed to the presence of substantial vestibular compensation in part of study participants in spite of the attempts to exclude such subjects. For a post hoc sensitivity analysis, subjects were excluded if their time to failure in the Standing on Foam test at baseline was ≥ 10 sec., a level which separated outliers from the bulk of low-performing subjects (7 in the placebo, 2 in each of the active treated groups). Their exclusion had no impact on the overall pattern of recovery in the Tandem Romberg test, but resulted in a larger differential in improvement between the AM-125 20 mg and placebo group at FUV2 and FUV3. Results reported below correspond to FUV3.

End point type	Post-hoc

End point timeframe:

From baseline to FUV3

Notes:

[9] - 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: In this entry major endpoints are presented. The final analysis did focus on the 10 mg and 20 mg cohorts. Therefore, the statistic for the 1 mg cohort is not presented here. For more information the reader can refer to the publication of the study or send a request to the sponsor.

End point values	Placebo	Intranasal AM-125, 10 mg	Intranasal AM-125, 20 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	32	30	
Units: seconds				
least squares mean (standard deviation)	7.9 (± 6.47)	9.7 (± 7.92)	12.2 (± 10.58)	

Statistical analyses

Statistical analysis title	Improvement in TRT between Placebo and AM-125
Comparison groups	Placebo v Intranasal AM-125, 20 mg

Number of subjects included in analysis	54
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.059 [10]
Method	Mixed models analysis

Notes:

[10] - Results are provided for AM-125 20mg vs . Placebo at FUV3

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline to end of study at all visits.

Adverse event reporting additional description:

Only adverse events related to the IMP AM-125 are reported here.
Other adverse events related to the surgery are not reported here.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	AM-125 1mg
Reporting group description: -	
Reporting group title	AM-125 10mg
Reporting group description: -	
Reporting group title	AM-125 20mg
Reporting group description: -	
Reporting group title	Oral Betahistine 16mg
Reporting group description: -	

Serious adverse events	Placebo	AM-125 1mg	AM-125 10mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 32 (0.00%)	0 / 9 (0.00%)	0 / 34 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	AM-125 20mg	Oral Betahistine 16mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 33 (0.00%)	0 / 16 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Placebo	AM-125 1mg	AM-125 10mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 32 (9.38%)	2 / 9 (22.22%)	1 / 34 (2.94%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 32 (0.00%)	1 / 9 (11.11%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 32 (0.00%)	1 / 9 (11.11%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 32 (0.00%)	0 / 9 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Transaminases abnormal			
subjects affected / exposed	0 / 32 (0.00%)	0 / 9 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 32 (0.00%)	1 / 9 (11.11%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Hypertension			
subjects affected / exposed	0 / 32 (0.00%)	1 / 9 (11.11%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 32 (0.00%)	2 / 9 (22.22%)	0 / 34 (0.00%)
occurrences (all)	0	2	0
Dysgeusia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 9 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 32 (0.00%)	0 / 9 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Mucosal dryness			

subjects affected / exposed	1 / 32 (3.13%)	0 / 9 (0.00%)	0 / 34 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Aphthous ulcer			
subjects affected / exposed	0 / 32 (0.00%)	0 / 9 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Nasal discomfort			
subjects affected / exposed	1 / 32 (3.13%)	1 / 9 (11.11%)	0 / 34 (0.00%)
occurrences (all)	1	2	0
Cough			
subjects affected / exposed	0 / 32 (0.00%)	0 / 9 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 32 (0.00%)	0 / 9 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Nasal crusting			
subjects affected / exposed	1 / 32 (3.13%)	0 / 9 (0.00%)	0 / 34 (0.00%)
occurrences (all)	1	0	0
Nasal dryness			
subjects affected / exposed	0 / 32 (0.00%)	1 / 9 (11.11%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Nasal mucosal disorder			
subjects affected / exposed	1 / 32 (3.13%)	0 / 9 (0.00%)	0 / 34 (0.00%)
occurrences (all)	1	0	0
Nasal pruritus			
subjects affected / exposed	0 / 32 (0.00%)	0 / 9 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Nasal ulcer			
subjects affected / exposed	1 / 32 (3.13%)	0 / 9 (0.00%)	0 / 34 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	0 / 32 (0.00%)	0 / 9 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Rash			

subjects affected / exposed	0 / 32 (0.00%)	0 / 9 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 9 (11.11%)	0 / 34 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	AM-125 20mg	Oral Betahistine 16mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 33 (15.15%)	3 / 16 (18.75%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 33 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 33 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 33 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Transaminases abnormal			
subjects affected / exposed	0 / 33 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 33 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Hypertension			
subjects affected / exposed	0 / 33 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 33 (3.03%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Dysgeusia			

subjects affected / exposed	1 / 33 (3.03%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 33 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Mucosal dryness			
subjects affected / exposed	0 / 33 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Aphthous ulcer			
subjects affected / exposed	0 / 33 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Nasal discomfort			
subjects affected / exposed	0 / 33 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Cough			
subjects affected / exposed	1 / 33 (3.03%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Epistaxis			
subjects affected / exposed	1 / 33 (3.03%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Nasal crusting			
subjects affected / exposed	0 / 33 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Nasal dryness			
subjects affected / exposed	0 / 33 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Nasal mucosal disorder			
subjects affected / exposed	0 / 33 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Nasal pruritus			
subjects affected / exposed	1 / 33 (3.03%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Nasal ulcer			

subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 16 (0.00%) 0	
Skin and subcutaneous tissue disorders Dermatitis contact subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	 0 / 33 (0.00%) 0 1 / 33 (3.03%) 1	 1 / 16 (6.25%) 1 0 / 16 (0.00%) 0	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 0 / 33 (0.00%) 0	 0 / 16 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 February 2019	The protocol amendment 1 was issued due to a request from the Belgian competent authority concerning the use of contraception and the definition of women of childbearing potential. The contraception methods of diaphragm with spermicide, male or female condoms with spermicide, or cervical cap were deleted. Criteria for excluding women with pregnancy, breast-feeding, child-bearing potential and unable/unwilling to use contraceptive methods also need to be checked at TV in addition to SV.
17 October 2019	The protocol amendment 2 was issued to facilitate subject recruitment as well as to avoid duplication of safety assessments as relevant new safety information was available. It included: -Extension of the subject population to include subjects who developed symptom following labyrinthectomy or vestibular neurectomy as the pathophysiology is the same (acute damage to vestibular nerve with one-sided loss of afferent neurotransmission from the inner ear to the brain). Modification of inclusion and exclusion criteria based on investigator feedback from sites after recruitment start to facilitate a smooth conduct of the study. Removal of two low/intermediate doses (2.5 and 5 mg) in Part A based on favorable safety outcomes in another study (AM 201 CL 18 01) with escalation of exactly the same IMP doses (1 to 20 mg t.i.d.) and the same treatment duration of 4 weeks.
07 September 2020	The protocol amendment 3 was based on the pre-planned interim analysis following completion of Part A: 10 mg dose was selected as the low dose and the 20 mg dose was selected as the high dose to be tested in Part B. The interim analysis for Part A confirmed the assumptions of the initial sample size calculation. The sample size was therefore not changed and remained 24 patients per treatment arm, 72 patients in total. The VRBQ was added to evaluate important aspects of dizziness impact.
23 December 2021	The protocol amendment 4 was issued to incorporate result of additional ad-hoc analyses following the completion of Part A. It was concluded that the Tandem Romberg test tends to be more challenging for patients and has a lower likelihood of being affected by a ceiling effect compared to the Standing on Foam test. Also, an efficacy endpoint at 6 weeks following surgery was considered more indicative of lasting improvement than an endpoint after 2 weeks only. Therefore, it was decided to switch the primary and key-secondary endpoints for the final statistical analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Limitations that may have affected the results of the primary efficacy endpoint included the small sample size and high placebo response.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/37026797