Clinical trial results:
A 6-month, prospective, randomized, multicenter, placebo-controlled safety study of OTO-104 given at 3-month intervals by intratympanic injection in subjects with unilateral Meniere's disease, followed by a 6-month open-label extension

Summary

EudraCT number	2014-001337-86
Trial protocol	GB
Global end of trial date	19 May 2016

Results information

Result version number	v1 (current)
This version publication date	13 December 2021
First version publication date	13 December 2021

Trial information

Trial identification

Sponsor protocol code	104-201403

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02265393
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Otonomy Inc
Sponsor organisation address	4796 Executive Drive, San Diego, United States, CA 92121
Public contact	Otonomy Medical Information, Otonomy Inc., medinfo@otonomy.com
Scientific contact	Otonomy Medical Information, Otonomy Inc, medinfo@otonomy.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	21 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 May 2016
Global end of trial reached?	Yes
Global end of trial date	19 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of the first part of the study was to evaluate the safety of 2 intratympanic doses of 12 mg OTO-104, compared with placebo, given at 3-month intervals in subjects with unilateral Meniere's disease.

The objective of the second part of the study was to continue to assess the safety of 2 intratympanic injections of 12 mg OTO-104 at 3 month intervals in an open-label phase.

Protection of trial subjects:

Subjects in this study were to receive up to 4 intratympanic injections spaced 3 months apart. Prior to each injection, a numbing cream (containing lidocaine and prilocaine) was applied to the subject's tympanic membrane to manage pain/discomfort associated with the injection.

One of the primary concerns identified prior to the study was the potential for tympanic membrane perforation because of the injection procedure itself as well as any other risks associated with the study. To that end, a data safety monitoring board was organized, had their first meeting prior to the 1st subject's 3rd injection and then quarterly thereafter to review the study progress and the evolving safety data. The DSMB could be convened as needed, which it was when there was a serious adverse event that occurred during a subject's second injection. At each meeting, the DSMB was charged with evaluating safety data to determine whether the study should continue and concluded each time that the study could continue.

Background therapy:

Subjects maintained their current standard-of-care treatment for Meniere's disease while on study, including but not limited to, low-salt diet, diuretic, and/or betahistine.

Evidence for comparator:

This was a safety study so there was no comparator.

Actual start date of recruitment	01 July 2014
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	United Kingdom: 128
Worldwide total number of subjects	128
EEA total number of subjects	128

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)	106
From 65 to 84 years	22
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Sixteen centers in the United Kingdom screened 144 subjects, with 128 randomized (103 to OTO-104; 25 subjects to placebo). In the second phase of the study all subjects received OTO-104 (n = 123; there were 5 discontinuations prior to the beginning of the second phase [Month 6].

Pre-assignment

Screening details:

Subjects enrolled in the study were required to have unilateral Meniere's disease as outlined by the American Academy of Otolaryngology – Head and Neck Surgery (AAO-HNS) Committee on Hearing and Equilibrium in 1995 (Committee on Hearing and Equilibrium, 1995). A total of 144 subjects were screened to enroll 128 subjects.

Period 1

Period 1 title	overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind[1]
Roles blinded	Subject, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Study site personnel, who were blinded to treatment assignment, provided the information (unique number) contained in the central randomization system notification to the unblinded qualified medical professional (QMP) responsible for preparing the syringe containing study drug. The QMP prepared the syringe from the contents of the study drug. The QMP prepared the syringe from the contents of the study drug package corresponding to the randomization system unique number.

Arms

Are arms mutually exclusive?	Yes
Arm title	OTO-104

Arm description:

OTO-104 (Dexamethasone suspension in a poloxamer 407 solution for intratympanic injection)

Arm type	Experimental
Investigational medicinal product name	Dexamethasone suspension in a poloxamer 407 solution
Investigational medicinal product code	OTO-104
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intratympanic use

Dosage and administration details:

The OTO-104 final product suspension for dosing was prepared by an unblinded qualified medical professional from 2 separate components, OTO-104 Diluent (1 vial) and OTO-104 Active (1 vial). An appropriate volume of OTO-104 Diluent was withdrawn and delivered into the OTO-104 Active vial to achieve a visually homogeneous suspension with a target drug concentration of 60 mg/mL. The subject is placed in a recumbent position with the treated ear upwards. The tympanic membrane is anesthetized by either covering the external surface of the posterior-inferior quadrant with topical lidocaine/prilocaine cream ([EMLA] cream) until the tympanic membrane is numb. The needle is inserted through the tympanic membrane with the bevel facing in an inferoposterior direction to a depth of approximately 2-3 mm just inferior to the round window niche, and with firm but gentle pressure, 0.2 mL is injected.

Arm title	Placebo

Arm description:

Poloxamer 407 solution

Arm type	Placebo

Investigational medicinal product name	Poloxamer 407
Investigational medicinal product code	P407
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intratympanic use

Dosage and administration details:

Placebo (P407; OTO-104 Diluent) was administered as a single, 0.2 mL intratympanic injection.

Notes:

[1] - The roles blinded appear to be inconsistent with a double blind trial.

Justification: Since the OTO-104 and placebo looked different (OTO-104 is a white suspension and placebo is clear), the investigator who administered the injection was unblinded. However, the other staff remained blinded since care was taken in preparation of the dosing syringe and examination of the ear post-injection. A blinding plan was created for each site prior to the first dose administration.

Number of subjects in period 1	OTO-104	Placebo
Started	103	25
Completed	97	24
Not completed	6	1
Physician decision	1	-
Consent withdrawn by subject	4	-
Lost to follow-up	1	-
subject refused IP	-	1

Baseline characteristics

Reporting groups	
Reporting group title	OTO-104
Reporting group description:	
OTO-104 (Dexamethasone suspension in a poloxamer 407 solution for intratympanic injection)	
Reporting group title	Placebo
Reporting group description:	
Poloxamer 407 solution	

Reporting group values	OTO-104	Placebo	Total
Number of subjects	103	25	128
Age categorical Units: Subjects			
Adults (18-64 years)	84	22	106
From 65-84 years	19	3	22
85 years and over	0	0	0
Age continuous			
The age if the subject when they signed the consent form.			
Units: years			
median	54	55	
full range (min-max)	21 to 78	31 to 75	-
Gender categorical			
The gender as collected at Screening.			
Units: Subjects			
Female	54	16	70
Male	49	9	58

Subject analysis sets	
Subject analysis set title	Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects who received at least one IT dose	

Reporting group values	Safety		
Number of subjects	128		
Age categorical Units: Subjects			
Adults (18-64 years)	106		
From 65-84 years	22		
85 years and over	0		
Age continuous			
The age if the subject when they signed the consent form.			
Units: years			
median	54.5		
full range (min-max)	21 to 78		

Gender categorical			
The gender as collected at Screening.			
Units: Subjects			
Female	70		
Male	58		

End points

End points reporting groups

Reporting group title	OTO-104
Reporting group description:	
OTO-104 (Dexamethasone suspension in a poloxamer 407 solution for intratympanic injection)	
Reporting group title	Placebo
Reporting group description:	
Poloxamer 407 solution	
Subject analysis set title	Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects who received at least one IT dose	

Primary: Audiometry - Shift in Pure Tone Average

End point title	Audiometry - Shift in Pure Tone Average[1]
End point description:	
Change from Baseline in Pure Tone Average (PTA) calculated as the mean of air conduction thresholds at 500, 1000, and 2000 Hz.	
End point type	Primary
End point timeframe:	
Up to 1 year	

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: The primary endpoints for this study were safety in nature and as such, no additional statistics were performed other than summary statistics.

End point values	OTO-104	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93[2]	24[3]		
Units: Pure Tone Average				
arithmetic mean (standard deviation)	-0.2 (± 15.07)	-1.5 (± 14.66)		

Notes:

[2] - Subjects with PTA measurements at Baseline and Month 12

[3] - Subjects with PTA measurements at Baseline and Month 12

Statistical analyses

No statistical analyses for this end point

Primary: Meniere's Symptom Questionnaire

End point title	Meniere's Symptom Questionnaire[4]
End point description:	
Change in Meniere's disease Questionnaire values; each category can be scored from 1 = none to 5 = extremely severe; a negative change = improvement.	
End point type	Primary
End point timeframe:	
Up to 1 Year	

Notes:

[4] - 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: The primary endpoints for this study were safety in nature and as such, no additional statistics were performed other than summary statistics.

End point values	OTO-104	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97[5]	25[6]		
Units: Score at Month 12				
median (full range (min-max))				
Vertigo	1.0 (1 to 5)	1.0 (1 to 4)		
Tinnitus	3.0 (1 to 5)	3.0 (1 to 4)		
Ear Fullness	2.0 (1 to 5)	2.0 (1 to 4)		
Hearing Difficulty	3.0 (1 to 5)	3.0 (2 to 4)		

Notes:

[5] - Subjects with a questionnaire at Month 12

[6] - Subjects with a questionnaire at Month 12

Statistical analyses

No statistical analyses for this end point

Primary: Tympanic Membrane Perforation

End point title	Tympanic Membrane Perforation[7]

End point description:

Perforations were rated as "Present" or "Not Present"; if a subject did not receive an otoscopy, then the perforation is listed as "Missing".

End point type	Primary

End point timeframe:

Up to 12 months; otoscopy examinations were performed at 3, 6, 9, 12 months in the ear that received the injection(s) at Baseline, Month 3, Month 6, and Month 9, respectively.

Notes:

[7] - 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: The primary endpoints for this study were safety in nature and as such, no additional statistics were performed other than summary statistics.

End point values	OTO-104	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103[8]	25[9]		
Units: ears				
Present	2	0		
Not Present	94	25		
Missing	7	0		

Notes:

[8] - OTO-104 subjects who had an Otoscopy at Baseline and last visit (up to Month 12).

[9] - Placebo subjects who had an Otoscopy at Baseline and last visit (up to Month 12).

Statistical analyses

No statistical analyses for this end point

Secondary: Tympanometry - Shift from Type A at Baseline

End point title	Tympanometry - Shift from Type A at Baseline

End point description:

Tympanometry assessments are used to assess the mobility and compliance of the tympanic membrane, pressure and volume in the middle ear, and function of the tympanic membrane, ossicles and eustachian tube. Type A is considered normal and the results presented here are for the percentage of treated ears that change from normal (Type A) at Baseline to another category.

End point type	Secondary

End point timeframe:

Up to 1 Year

End point values	OTO-104	Placebo	Safety	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	92[10]	22[11]	109[12]	
Units: Subject				
Number with shift from Type A at Baseline	2	1	4	

Notes:

[10] - Subjects randomized to OTO-104 with a tympanometry at Baseline and one at Month 6 after 2 injections

[11] - Subjects randomized to Placebo with a tympanometry at Baseline and one at Month 9 after 2 injections

[12] - Subjects with a tympanometry at Baseline and one at Month 12 after 4 injections

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Adverse events recorded at 6 months	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0
Reporting groups	
Reporting group title	OTO-104
Reporting group description: Dexamethasone suspension in a poloxamer 407 solution for intratympanic injection	
Reporting group title	Placebo
Reporting group description: Poloxamer 407 solution	

Serious adverse events	OTO-104	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 103 (2.91%)	2 / 25 (8.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bowel Cancer	Additional description: Moderate and not related.		
alternative assessment type: Systematic			
subjects affected / exposed	1 / 103 (0.97%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Laceration	Additional description: Laceration to right hand ring finger. Severe and not related.		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 103 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dizziness	Additional description: Severe and related.		
alternative assessment type: Systematic			

subjects affected / exposed	1 / 103 (0.97%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Hearing Loss	Additional description: Unilateral Deafness. Severe, definitely related.		
alternative assessment type: Systematic			
subjects affected / exposed	1 / 103 (0.97%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting	Additional description: Severe and definitely related.		
alternative assessment type: Systematic			
subjects affected / exposed	1 / 103 (0.97%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis	Additional description: Severe. Not related.		
alternative assessment type: Systematic			
subjects affected / exposed	1 / 103 (0.97%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back Pain	Additional description: Moderate and not related.		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 103 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	OTO-104	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	56 / 103 (54.37%)	5 / 25 (20.00%)	
Nervous system disorders			

Migraine			
subjects affected / exposed	6 / 103 (5.83%)	0 / 25 (0.00%)	
occurrences (all)	6	0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	15 / 103 (14.56%)	2 / 25 (8.00%)	
occurrences (all)	15	2	
Dizziness			
subjects affected / exposed	10 / 103 (9.71%)	1 / 25 (4.00%)	
occurrences (all)	10	1	
Meniere's disease			
subjects affected / exposed	13 / 103 (12.62%)	0 / 25 (0.00%)	
occurrences (all)	13	0	
Tinnitus			
subjects affected / exposed	4 / 103 (3.88%)	2 / 25 (8.00%)	
occurrences (all)	4	2	
Ear pain			
subjects affected / exposed	8 / 103 (7.77%)	1 / 25 (4.00%)	
occurrences (all)	8	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 June 2014	Corrected the Visit Number for the Meniere's symptom questionnaire from Visit 1 to Visit 2 (Synopsis, Page 11). Modified the unblinding procedure to clarify that the physician administering the study drug is unblinded at the time of injection as well as accessing the study drug preparation records if the physician administering the study drug is not available or does not recollect the treatment administered (Section 5.3, Blinding, Page 19). Replace "violation" with "deviation" (Section 7.1, Proscribed Therapy During the Study Period, pg. 20; Section 7.2, Symptomatic Relief Medications, pg. 20; Section 11.4, Subject Demographics, Baseline Disease Status, and Disposition, pg. 30 Modified the number and description of the responses to the Meniere's Symptom Questionnaire (Section 8.2.6, Meniere's Symptom Questionnaire, pg. 24).
02 October 2015	Updated Medical Monitor contact to include Otonomy Drug Safety contact (Section 9.3, Contacting Sponsor Regarding Safety, page 28) Included the following additional text in bold per DSMB recommendation after SAE: "Using the tuberculin syringe pre-loaded with OTO-104 or placebo and equipped with a 26 gauge or 25 gauge needle, insert the needle through the tympanic membrane with the bevel facing in an inferoposterior direction to a depth of approximately 2-3 mm just inferior to the round window niche, and with firm but gentle pressure, inject 0.2 mL, taking care not to insert the needle further than necessary (Section 6.1, Study Drug Administration, page 19) Time and Events Table/Study Flow Chart to include the C-SSRS assessment for Visits 4-6 and included a footnote (Table 1, pg. 13-14) . Included the C-SSRS guidance (Section 8.2.7 C-SSRS Assessment, pg. 26) Section changed for Safety stopping rules with the addition of C-SSRS (Changed from Section 8.2.7 to 8.2.8, page 26) Included C-SSRS in the Safety Evaluation section (Section 11.7, page 35)Included C-SSRS guidance (Sections 11.7.6, 11.7.6.1, 11.7.6.2) DSMB section referenced the incorrect section for the safety stopping rules: "Should any untoward safety issue be observed, or any of the stopping rules outlined in Section 8.2.8 be invoked, the DSMB will schedule an immediate meeting to review the relevant safety data" (Section 8.2.8, page 40).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported