Clinical trial results:
A prospective, randomized, double blind, placebo-controlled, multicenter, Phase 3 efficacy and safety study of OTO-104 given as a single intratympanic injection in subjects with unilateral Meniere's disease.

Summary

EudraCT number	2018-001464-35
Trial protocol	GB ES BE IT
Global end of trial date	22 December 2020

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022

Trial information

Trial identification

Sponsor protocol code	104-201811

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03664674
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Otonomy, Inc.
Sponsor organisation address	4796 Executive Drive, San Diego, United States, 92121
Public contact	Medical Information, Otonomy, Inc., 1 6193232200,
Scientific contact	Medical Information, Otonomy, Inc., 1 844-686-4636, 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	25 February 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 December 2020
Global end of trial reached?	Yes
Global end of trial date	22 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the efficacy of OTO-104 in subjects with Meniere's disease, as measured by the number of definitive vertigo days (DVD) at Week 12 (the 4-week interval from Week 9 through Week 12).

Protection of trial subjects:

The study was conducted in accordance with current Good Clinical Practice (GCP). This study was undertaken only after a designated Independent Ethics Committee (IEC) had fully approved the protocol and the sponsor had received a copy of the approval. Written informed consent was obtained from each subject prior to the performance of any study-specific procedures according to local requirements after the nature of the study had been fully explained. Each subject was informed that they were free not to participate in the study and that they could withdraw consent to participate at any time. Subjects who chose to participate signed an informed consent document. Lastly, to decrease pain from the injection procedure, the tympanic membrane was anesthetized with a topical lidocaine/prilocaine cream.

Background therapy:

Subjects were allowed to continue symptomatic relief medications for Ménière's disease symptoms, prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications they were on when they started in the trial. They were requested to maintain the same regimen throughout the study.

Evidence for comparator:

The study used a placebo control, which the sponsor believed was the most direct way to measure the effect of the investigational product. In addition, the following points support use of a placebo control:

- There is no drug product injected in the ear that is approved for the treatment of Ménière's disease. While ear injections of steroid solutions are used in clinical practice, there is need for research to find out if they work.
- Betahistine has been approved by certain health authorities and is commonly used to treat Ménière's disease. It may have been an active control to compare its effect versus OTO-104 however, a review of previous trials conducted with betahistine concluded that there is "insufficient evidence to say whether betahistine has any effect on Ménière's disease." In addition, a more recent trial concluded that in the "randomised, placebo-controlled study described, the effects of two different doses of betahistine could not be distinguished from a patient reported effect caused by placebo intervention." Therefore, its value as an active control is unknown.
- Notwithstanding, subjects were recommended to continue taking medications they were taking before the study started. This could have included betahistine, diuretics (water pills), and/or a low salt diet (in other words, their standard of care).
- The option of a sham injection of air or the patient not receiving any injection as a control was also considered. However, there was concern that this could accidentally "unblind" the patient (the patient would know they did not receive anything) if they could not tell if there was material in their ear. This could make it difficult to properly evaluate their vertigo, which could affect the study results.

Actual start date of recruitment	01 October 2018
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	Poland: 60
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	United Kingdom: 16
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	Germany: 15
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	United States: 21
Country: Number of subjects enrolled	Turkey: 11
Worldwide total number of subjects	148
EEA total number of subjects	100

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)	108
From 65 to 84 years	40
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Overall, 66 investigators were approved in Belgium, Germany, Italy, Poland, Spain, Turkey, United States, and United Kingdom) to conduct this study. Forty-two investigators enrolled subjects. First subject was randomized 14 December 2018; Last subject was randomized 29 September 2020.

Pre-assignment

Screening details:

A total of 317 subjects registered for this study and signed informed consent. Of these, 149 subjects were randomized and 148 subjects received study drug. The most common reason for screen failure was that there was not a sufficient number of definitive vertigo days in the 28-day lead-in period.

Period 1

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

Blinding implementation details:

A treatment syringe (OTO-104 or placebo) was pre-loaded by an unblinded person. Each syringe was prepared to prevent visualization of syringe contents by all other study staff through the use of a syringe overlabel. Any interaction with subjects with regard to the collection, review or discussion of study assessments, with the exception of otoscopic exams, was done by the study coordinator, audiologist or someone other than the person who prepared the syringe and the physician who administered.

Arms

Are arms mutually exclusive?	Yes
Arm title	OTO-104

Arm description:

Dexamethasone suspension in an aqueous solution containing poloxamer 407. Poloxamer 407 has thermosensitive properties such that it is a liquid at room temperature and will gel when exposed to body temperature when injected into the middle ear.

Arm type	Experimental
Investigational medicinal product name	OTO-104
Investigational medicinal product code	
Other name	Dexamethasone
Pharmaceutical forms	Powder and solution for suspension for injection
Routes of administration	Intratympanic use

Dosage and administration details:

OTO-104 12 mg was administered as a single, 0.2 mL intratympanic injection of 60 mg/mL OTO-104. The OTO-104 final product suspension for dosing was prepared from 2 separate components: 16% poloxamer 407 solution (1 vial needed) and OTO-104 Active (1 vial needed). An appropriate volume of 16% poloxamer solution was withdrawn and delivered into the OTO 104 Active vial to achieve a visually homogeneous suspension of a target drug concentration of 60 mg/mL.

Arm title	Placebo

Arm description:

The placebo was an aqueous solution of poloxamer 407.

Arm type	Placebo

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

Dosage and administration details:

Placebo 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	73	75
Completed	73	75

Period 2

Period 2 title	Follow-Up (Week 12)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind[2]
Roles blinded	Subject, Monitor, Data analyst, Assessor

Blinding implementation details:

Any interaction with subjects with regard to the collection, review or discussion of study assessments, with the exception of otoscopic exams, was done by the study coordinator, audiologist or someone other than the person who prepared the syringe and the physician who administered the injection. As the injection was give at the Baseline visit, no further IMP was administered.

Arms

Are arms mutually exclusive?	Yes
Arm title	OTO-104

Arm description:

Dexamethasone suspension in an aqueous solution containing poloxamer 407. Poloxamer 407 has thermosensitive properties such that it is a liquid at room temperature and will gel when exposed to body temperature when injected into the middle ear.

Arm type	Experimental
Investigational medicinal product name	OTO-104
Investigational medicinal product code	
Other name	Dexamethasone
Pharmaceutical forms	Powder and solution for suspension for injection
Routes of administration	Intratympanic use

Dosage and administration details:

OTO-104 12 mg was administered as a single, 0.2 mL intratympanic injection of 60 mg/mL OTO-104. The OTO-104 final product suspension for dosing was prepared from 2 separate components: 16% poloxamer 407 solution (1 vial needed) and OTO-104 Active (1 vial needed). An appropriate volume of 16% poloxamer solution was withdrawn and delivered into the OTO 104 Active vial to achieve a visually

homogeneous suspension of a target drug concentration of 60 mg/mL.

Arm title	Placebo
Arm description:	
The placebo was an aqueous solution of poloxamer 407.	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	Poloxamer 407 solution
Pharmaceutical forms	Solution for injection
Routes of administration	Intratympanic use
Dosage and administration details:	
Placebo was administered as a single, 0.2 mL intratympanic injection.	

Notes:

[2] - 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 2	OTO-104	Placebo
Started	73	75
Completed	70	73
Not completed	3	2
Consent withdrawn by subject	2	-
Physician decision	-	1
Adverse event, non-fatal	1	1

Baseline characteristics

Reporting groups

Reporting group title	OTO-104

Reporting group description:

Dexamethasone suspension in an aqueous solution containing poloxamer 407. Poloxamer 407 has thermosensitive properties such that it is a liquid at room temperature and will gel when exposed to body temperature when injected into the middle ear.

Reporting group title	Placebo

Reporting group description:

The placebo was an aqueous solution of poloxamer 407.

Reporting group values	OTO-104	Placebo	Total
Number of subjects	73	75	148
Age categorical			
Units: Subjects			
Adults (18-64 years)	51	57	108
From 65-84 years	22	18	40
85 years and over	0	0	0
Age continuous			
Inclusion age for this study was 18 to 85 years, inclusive.			
Units: years			
median	57.0	57.0	
full range (min-max)	27 to 75	26 to 83	-
Gender categorical			
Both males and females were allowed in this study.			
Units: Subjects			
Female	44	44	88
Male	29	31	60
Duration of Meniere's Disease			
The length of time since diagnosis			
Units: Subjects			
<=5 years	61	53	114
6-10 years	9	13	22
11-15 years	0	4	4
>15 years	3	5	8

Subject analysis sets

Subject analysis set title	Intent to Treat Analysis Set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The intent to treat analysis set included all randomized subjects all who receive study drug. Subjects were included in the treatment group to which
they were randomized regardless of the actual study drug received.

Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population included all subjects who received study drug. Note: The safety analysis set populations were displayed by the treatment the subject received.

Reporting group values	Intent to Treat Analysis Set	Safety Analysis Set	
Number of subjects	148	148	
Age categorical Units: Subjects			
Adults (18-64 years)	108	108	
From 65-84 years	40	40	
85 years and over	0	0	
Age continuous			
Inclusion age for this study was 18 to 85 years, inclusive.			
Units: years			
median	57.0	57.0	
full range (min-max)	26 to 83	26 to 83	
Gender categorical			
Both males and females were allowed in this study.			
Units: Subjects			
Female	86	88	
Male	58	60	
Duration of Meniere's Disease			
The length of time since diagnosis			
Units: Subjects			
<=5 years	111	114	
6-10 years	21	22	
11-15 years	4	4	
>15 years	8	8	

End points

End points reporting groups

Reporting group title	OTO-104
Reporting group description:	
Dexamethasone suspension in an aqueous solution containing poloxamer 407. Poloxamer 407 has thermosensitive properties such that it is a liquid at room temperature and will gel when exposed to body temperature when injected into the middle ear.	
Reporting group title	Placebo
Reporting group description:	
The placebo was an aqueous solution of poloxamer 407.	
Reporting group title	OTO-104
Reporting group description:	
Dexamethasone suspension in an aqueous solution containing poloxamer 407. Poloxamer 407 has thermosensitive properties such that it is a liquid at room temperature and will gel when exposed to body temperature when injected into the middle ear.	
Reporting group title	Placebo
Reporting group description:	
The placebo was an aqueous solution of poloxamer 407.	
Subject analysis set title	Intent to Treat Analysis Set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The intent to treat analysis set included all randomized subjects all who receive study drug. Subjects were included in the treatment group to which they were randomized regardless of the actual study drug received.	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population included all subjects who received study drug. Note: The safety analysis set populations were displayed by the treatment the subject received.	

Primary: 28-Day Average DVD at Week 12 (month 3)

End point title	28-Day Average DVD at Week 12 (month 3)
End point description:	
End point type	Primary
End point timeframe:	
Month 3 - defined as the 4 week interval from Week 9 and Week 12.	

End point values	OTO-104	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	75		
Units: Days				
least squares mean (confidence interval 95%)	2.869 (2.109 to 3.903)	3.577 (2.641 to 4.844)		

Statistical analyses

Statistical analysis title	Analysis of DVD Count at Week 12

Statistical analysis description:

The count of definitive vertigo days for Week 12 was determined during the 4-week period between Weeks 9 and 12. A definitive vertigo day was any day the subject recorded a vertigo episode lasting at least 20 minutes and corresponding to a Vertigo Severity Score of 2 or more. Negative binomial model including coefficients for randomized treatment, sex, and lead-in period definitive vertigo days standardized to 28 days as a covariate.

Comparison groups	OTO-104 v Placebo
Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.312 [2]
Method	Generalized Linear Model – Neg Binomial
Parameter estimate	Mean difference (final values)
Point estimate	-0.221
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.648
upper limit	0.207
Variability estimate	Standard error of the mean
Dispersion value	0.218

Notes:

[1] - Generalized Linear Model – Negative Binomial Regression Model with count data by subject transformed using the log-link function.

[2] - The parameter estimate and confidence interval results back-transform to the ratio of adjusted mean definitive vertigo days (OTO-104/Placebo) to be 0.802 (0.523, 1.230).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded as observed or reported during or after dosing up to the final visit (Day 84).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	OTO-104

Reporting group description:

Dexamethasone suspension in an aqueous solution containing poloxamer 407. Poloxamer 407 has thermosensitive properties such that it is a liquid at room temperature and will gel when exposed to body temperature when injected into the middle ear.

Reporting group title	Placebo

Reporting group description:

The placebo was an aqueous solution of poloxamer 407.

Serious adverse events	OTO-104	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 73 (2.74%)	2 / 75 (2.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 73 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniere's disease			
subjects affected / exposed	0 / 73 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Uterine haemorrhage			
subjects affected / exposed	1 / 73 (1.37%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

COVID-19			
subjects affected / exposed	1 / 73 (1.37%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	OTO-104	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 73 (35.62%)	27 / 75 (36.00%)	
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	2 / 73 (2.74%)	0 / 75 (0.00%)	
occurrences (all)	2	0	
Fall			
subjects affected / exposed	1 / 73 (1.37%)	2 / 75 (2.67%)	
occurrences (all)	1	2	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 73 (2.74%)	0 / 75 (0.00%)	
occurrences (all)	2	0	
Ear and labyrinth disorders			
Meniere's disease			
subjects affected / exposed	6 / 73 (8.22%)	6 / 75 (8.00%)	
occurrences (all)	6	6	
Tinnitus			
subjects affected / exposed	5 / 73 (6.85%)	0 / 75 (0.00%)	
occurrences (all)	5	0	
Vertigo			
subjects affected / exposed	4 / 73 (5.48%)	7 / 75 (9.33%)	
occurrences (all)	4	7	
Ear discomfort			
subjects affected / exposed	2 / 73 (2.74%)	2 / 75 (2.67%)	
occurrences (all)	2	2	
Ear pain			

subjects affected / exposed	1 / 73 (1.37%)	4 / 75 (5.33%)	
occurrences (all)	1	4	
Tympanic membrane disorder			
subjects affected / exposed	0 / 73 (0.00%)	2 / 75 (2.67%)	
occurrences (all)	0	2	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	2 / 73 (2.74%)	2 / 75 (2.67%)	
occurrences (all)	2	2	
Nasopharyngitis			
subjects affected / exposed	1 / 73 (1.37%)	2 / 75 (2.67%)	
occurrences (all)	1	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 August 2019	Version 2.0 implemented the following substantive changes: • Clarified that subjects should continue to record their daily vertigo experience until Day 84 even if Visit 5 was performed early (out of window) • Increased the number of study sites from approximately 50 to 60 • Increased upper age limit from 75 to 85 • Clarified that unblinding could be done through the study randomization system • Clarified the topical lidocaine included lidocaine spray and that other related anesthetics may have been used • Clarified that tympanometry did not need to be performed if the examiner decided that there was a contraindication to performing the procedure, such as tympanic perforation • Corrected the protocol to indicate that at Screening audiograms should also have been conducted at 250 and 3000 Hz • Clarified that medical staff who perform the otoscopic examinations did not need to be physicians, but should have been medical personnel who were experienced in performing otoscopic examinations • Removed the Completer analysis set to be consistent with the draft statistical analysis plan
30 July 2020	Version 3.0 implemented the following substantive changes: • Updated number of enrolled subjects from 160 to approximately 142 subjects • Revised sample size calculation based on Negative Binomial model at Week 12 (replacing the generalized Poisson model) • Analysis sets definitions revised and reflected primary analysis at Week 12 (the 4-week [28 day] interval from Week 9 to Week 12) and clarified when the ITT analysis set would be used. • For subgroup analyses, added age categories at the higher end • For subgroup analyses, added betahistine use as a subgroup • Updated the primary efficacy endpoint to the 28-day average DVD at Week 12 (rather than number of DVD at Week 12) • Added 2 new secondary endpoints (75% and 50% reduction from baseline in DVD) and refined the definition of previously named secondary endpoints • Added 1 new exploratory endpoint and refined the definition of previously named secondary endpoints • Described gate-keeping procedure to control the Type I error

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported