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 Ménière's disease.

Summary

EudraCT number	2015-004496-71
Trial protocol	GB BE DE IT
Global end of trial date	31 August 2017

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	104-201508

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02717442
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 Center, Otonomy Inc., medinfo@otonomy.com
Scientific contact	Otonomy Medical Information Center, 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	29 March 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 August 2017
Global end of trial reached?	Yes
Global end of trial date	31 August 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To confirm the efficacy of OTO-104 in subjects with Ménière'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 contained a placebo control, which the sponsor believed is the most direct way to measure the effect of this investigational product. In addition, the following considerations would also lead to the conclusion that a placebo control is appropriate:

- There is no drug product administered intratympanically that is approved for the treatment of Ménière's disease. While intratympanic steroid solutions are used in clinical practice, there is need for additional clinical research to support their effectiveness. In addition, the intratympanic administration of gentamicin acts through an ototoxic effect and its use is typically restricted in Ménière's disease patients with residual hearing.
- Betahistine is approved and widely used for Ménière's disease, although a Cochrane Review concludes that there is "insufficient evidence to say whether betahistine has any effect on Ménière's disease". In addition, a recent article in The BMJ 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 are recommended to continue on medications they are on prior to the study start, which may include betahistine, diuretics, and/or a low salt diet (i.e., their standard of care). The requirement is simply that they must have the requisite number of definitive vertigo days in order to be randomized.
- The option of a sham injection (i.e., air) was also considered. However, there was concern that this could inadvertently "unblind" the subject if there were no perception of material in the ear.

Actual start date of recruitment	21 March 2016
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: 62
Country: Number of subjects enrolled	United Kingdom: 49
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Germany: 28
Country: Number of subjects enrolled	Italy: 18
Worldwide total number of subjects	174
EEA total number of subjects	174

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)	144
From 65 to 84 years	30
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Overall, 57 investigators were approved in Europe (Belgium, France, Germany, Italy, Poland, United Kingdom) were approved to conduct this study. Forty-nine investigators enrolled subjects. First subject was randomized 21 March 2016; Last subject was randomized 22 August 2017.

Pre-assignment

Screening details:

A total of 360 subjects registered for this study and signed informed consent. Of these, 176 subjects were randomized and 174 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, Carer, 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:

0.2 mL of a 6% suspension of dexamethasone in poloxamer 407 aqueous solution

Arm type	Experimental
Investigational medicinal product name	OTO-104
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intratympanic use

Dosage and administration details:

Subjects are administered the single intratympanic injection at baseline.

Arm title	Placebo

Arm description:

0.2 mL poloxamer 407 aqueous solution

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intratympanic use

Dosage and administration details:

Subjects are administered a single intratympanic injection at baseline.

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	86	88
Completed	86	88

Period 2

Period 2 title	Follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind[2]
Roles blinded	Subject, Monitor, Carer, Assessor

Blinding implementation details:

This period is comprised of all post-Baseline clinic visits. Because treatment was administered one time at the Baseline visit, the only blinding detail that is relevant is that only the unblinded staff member can perform the otoscopic examination. Any interaction with subjects with regard to the collection, review or discussion of study assessments, was done by someone other than the unblinded person who prepared the syringe and the investigator who administered the dose at the Baseline visit

Arms

Are arms mutually exclusive?	Yes
Arm title	OTO-104

Arm description:

0.2 mL of a 6% suspension of dexamethasone in poloxamer 407 aqueous solution

Arm type	Experimental
Investigational medicinal product name	OTO-104
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intratympanic use

Dosage and administration details:

There is no drug administered during the follow-up period. Subjects efficacy and safety are attributed to the single dose administered at baseline.

Arm title	Placebo

Arm description:

0.2 mL poloxamer 407 aqueous solution

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intratympanic use

Dosage and administration details:

There is no drug administered during the follow-up period. Subjects efficacy and safety are attributed to the single dose administered at baseline.

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	86	88
Completed	53	59
Not completed	34	29
Reason for discontinuation not stated	4	-
Study terminated by Sponsor	30	29
Joined	1	0
Subject randomized but not treated	1	-

Baseline characteristics

Reporting groups	
Reporting group title	OTO-104
Reporting group description:	
0.2 mL of a 6% suspension of dexamethasone in poloxamer 407 aqueous solution	
Reporting group title	Placebo
Reporting group description:	
0.2 mL poloxamer 407 aqueous solution	

Reporting group values	OTO-104	Placebo	Total
Number of subjects	86	88	174
Age categorical Units: Subjects			
Adults (18-64 years)	72	72	144
From 65-84 years	14	16	30
Age continuous			
Age in years			
Units: years arithmetic mean standard deviation	 51.8 ± 12.13	 52.6 ± 13.24	 -
Gender categorical Units: Subjects			
Female	44	48	92
Male	42	40	82
Race Units: Subjects			
White	82	82	164
Black or African American	0	0	0
Asian	1	1	2
Not Applicable	3	5	8

Subject analysis sets	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All randomized subjects that received study drug (OTO-104 or placebo)	
Subject analysis set title	Full Analysis Set-1
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects who were randomized, received study drug, had a baseline definitive vertigo measurement for the 4-week lead-in period and at least one 4-week definitive vertigo measurement post-baseline, i.e., at least 1 post-baseline daily diary entry.	

Reporting group values	Safety Analysis Set	Full Analysis Set-1	
Number of subjects	174	174	

Age categorical Units: Subjects			
Adults (18-64 years)	144	144	
From 65-84 years	30	30	
Age continuous			
Age in years			
Units: years			
arithmetic mean	52.2	52.2	
standard deviation	± 12.67	± 12.67	
Gender categorical Units: Subjects			
Female	92	92	
Male	82	82	
Race Units: Subjects			
White	164	164	
Black or African American	0	0	
Asian	2	2	
Not Applicable	8	8	

End points

End points reporting groups

Reporting group title	OTO-104
Reporting group description:	
0.2 mL of a 6% suspension of dexamethasone in poloxamer 407 aqueous solution	
Reporting group title	Placebo
Reporting group description:	
0.2 mL poloxamer 407 aqueous solution	
Reporting group title	OTO-104
Reporting group description:	
0.2 mL of a 6% suspension of dexamethasone in poloxamer 407 aqueous solution	
Reporting group title	Placebo
Reporting group description:	
0.2 mL poloxamer 407 aqueous solution	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All randomized subjects that received study drug (OTO-104 or placebo)	
Subject analysis set title	Full Analysis Set-1
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects who were randomized, received study drug, had a baseline definitive vertigo measurement for the 4-week lead-in period and at least one 4-week definitive vertigo measurement post-baseline, i.e., at least 1 post-baseline daily diary entry.	

Primary: Definitive Vertigo Day

End point title	Definitive Vertigo Day
End point description:	
A Definitive Vertigo Day (DVD) was defined as a day where the subject recorded at least 1 vertigo episode lasting at least 20 minutes corresponding to a Vertigo Severity Score of 2 or more. If multiple episodes occurred on a given day, subjects were instructed to record the Vertigo Severity Score for the worst episode experienced during the day.	
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	86	88		
Units: Day				
arithmetic mean (confidence interval 95%)	2.336 (1.747 to 3.125)	3.549 (2.763 to 4.560)		

Statistical analyses

Statistical analysis title	Generalized Poisson Linear Mixed Model

Statistical analysis description:

The model included fixed effects for randomized treatment group (OTO 104 vs placebo), sex (male vs female), study week (4, 8, 12), a treatment group by study week interaction, and the count of lead-in period DVD standardized to 28 days as a covariate. Study week was modeled as a categorical variable. The model also included a random intercept to account for the longitudinal design; an offset for the log of the number of daily diary entries recorded for each 4-week post-baseline period was added

Comparison groups	OTO-104 v Placebo
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.029
Method	Poisson

Notes:

[1] - The count of DVD at each 4-week study period standardized to 28 days was summarized using descriptive statistics. In addition, the count of DVD at each 4-week study period was summarized (not standardized to 28 days) descriptively. The ratio of the adjusted means from the model comparing OTO-104 to placebo at Week 12, the corresponding 95% CI, and p-value was presented.

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	18.1

Reporting groups

Reporting group title	OTO-104

Reporting group description:

0.2 mL of a 6% suspension of dexamethasone on poloxamer 407 aqueous solution

Reporting group title	Placebo

Reporting group description:

0.2 mL poloxamer 407 aqueous solution

Serious adverse events	OTO-104	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 86 (2.33%)	0 / 88 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Head injury	Additional description: The subject was admitted to the hospital 2 days after collapsing and hitting his head;. the cause of collapse was unknown; no symptoms to suggest the collapse was related to inner ear disorder; considered not related to study drug; subject completed		
subjects affected / exposed	1 / 86 (1.16%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis	Additional description: Subject had 2 hospitalisations during the study due to symptoms of cholecystitis. After the second hospitalization, the subject was placed on a waiting list for an elective cholecystectomy. The event was not considered related to study drug.		
subjects affected / exposed	1 / 86 (1.16%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 2	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	41 / 86 (47.67%)	20 / 88 (22.73%)	
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 86 (10.47%)	4 / 88 (4.55%)	
occurrences (all)	9	4	
Dizziness			
subjects affected / exposed	7 / 86 (8.14%)	2 / 88 (2.27%)	
occurrences (all)	7	2	
Ear and labyrinth disorders			
Meniere's disease			
subjects affected / exposed	5 / 86 (5.81%)	1 / 88 (1.14%)	
occurrences (all)	5	1	
Tinnitus			
subjects affected / exposed	4 / 86 (4.65%)	2 / 88 (2.27%)	
occurrences (all)	4	2	
Vertigo			
subjects affected / exposed	3 / 86 (3.49%)	2 / 88 (2.27%)	
occurrences (all)	3	2	
Ear discomfort			
subjects affected / exposed	2 / 86 (2.33%)	2 / 88 (2.27%)	
occurrences (all)	2	2	
Ear pain			
subjects affected / exposed	3 / 86 (3.49%)	3 / 88 (3.41%)	
occurrences (all)	3	3	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	3 / 86 (3.49%)	2 / 88 (2.27%)	
occurrences (all)	3	2	
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	3 / 86 (3.49%)	1 / 88 (1.14%)	
occurrences (all)	3	1	
Infections and infestations			
Nasopharyngitis			

subjects affected / exposed occurrences (all)	2 / 86 (2.33%) 2	3 / 88 (3.41%) 3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 October 2015	Added EudraCT Number and modified storage condition of the drug to be refrigerated as opposed to frozen.
13 January 2016	- Additional exclusion criteria to hypersensitivity to dexamethasone or any of the OTO-104 excipients. - Modified Section 1.1, Study Rationale to include rationale for dose selection. - Modified statement regarding contacting the medical monitor if an unblinding has occurred. - Changed pharmacovigilance vendor, and therefore contacts were updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported