Clinical trial results:
A 6-MONTH, MULTICENTER, PHASE 3, OPEN-LABEL EXTENSION SAFETY STUDY OF OTO-104 GIVEN AT 3-MONTH INTERVALS BY INTRATYMPANIC INJECTION IN SUBJECTS WITH UNILATERAL MENIERE'S DISEASE

Summary

EudraCT number	2016-000766-29
Trial protocol	GB BE DE IT
Global end of trial date	05 September 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	104-201610

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02768662
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., medinfo@otonomy.com
Scientific contact	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	08 June 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 September 2017
Global end of trial reached?	Yes
Global end of trial date	05 September 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The objective is to assess the safety of repeat intratympanic injections of 12 mg OTO-104 at 3-month intervals in an open-label study in subjects with unilateral Meniere's disease.

Protection of trial subjects:

Not Applicable

Background therapy:

Subjects were permitted to continue medications for relief of symptoms related to Meniere's disease during the course of the study. Intermittent use of vestibular suppressants and anti-emetics was allowed as symptomatic relief medications. Subjects were allowed to take betahistine as well.

Evidence for comparator:

Not Applicable - no comparator

Actual start date of recruitment	20 July 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	United Kingdom: 83
Country: Number of subjects enrolled	Poland: 23
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 17
Country: Number of subjects enrolled	Italy: 9
Worldwide total number of subjects	142
EEA total number of subjects	59

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)	123
From 65 to 84 years	19
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a 6-month, multicenter, Phase 3, open-label extension safety study in subjects with unilateral Meniere's disease that had previously completed the Phase 2 (104-201403) or Phase 3 (104-201508) studies.

Pre-assignment

Screening details:

Subjects that completed one of the prior studies were asked if they wanted to participate in this study and if so, they signed an informed consent.

Period 1

Period 1 title	Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This was an open-label study and therefore, no blinding was required.

Arms

Arm title	OTO-104

Arm description:

dexamethasone suspension in a solution of poloxamer 407

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:

The tympanic membrane was anesthetized by covering the external surface of the inferior-posterior quadrant with topical lidocaine or lidocaine/prilocaine cream. 200 microliters of a 6% w/v suspension of dexamethasone (12 mg) was administered via intratympanic injection by inserting the needle into the inferior-posterior quadrant of the tympanic membrane at the level of the round window.

Number of subjects in period 1	OTO-104
Started	142
Completed	90
Not completed	52
Consent withdrawn by subject	4
Subject received saccotomy	1
Adverse event, non-fatal	1
Missing reason for discontinuation	1
Study terminated by sponsor	43
Lost to follow-up	2

Baseline characteristics

Reporting groups

Reporting group title	Treatment

Reporting group description:

All subjects that received at least one intratympanic injection of OTO-104.

Reporting group values	Treatment	Total	
Number of subjects	142	142	
Age categorical Units: Subjects			
Adults (18-64 years)	123	123	
From 65-84 years	19	19	
Gender categorical Units: Subjects			
Female	77	77	
Male	65	65	

Subject analysis sets

Subject analysis set title	Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety analysis set included all subjects who received at least one dose of study drug.

Reporting group values	Safety		
Number of subjects	142		
Age categorical Units: Subjects			
Adults (18-64 years)	123		
From 65-84 years	19		
Gender categorical Units: Subjects			
Female	77		
Male	65		

End points

End points reporting groups

Reporting group title	OTO-104
Reporting group description: dexamethasone suspension in a solution of poloxamer 407	
Subject analysis set title	Safety
Subject analysis set type	Safety analysis
Subject analysis set description: The safety analysis set included all subjects who received at least one dose of study drug.	

Primary: Tympanic Membrane Perforation

End point title	Tympanic Membrane Perforation[1]
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 6 months; otoscopy examinations were performed at 3 and 6 months in the ear that received the injection(s).	

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 endpoint for this study was safety in nature and as such, no additional statistics were performed other than summary statistics.

End point values	OTO-104			
Subject group type	Reporting group			
Number of subjects analysed	142			
Units: ears				
Present	0			
Not Present	92			
Missing	50			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day 1 to end of study, which could have been up to Month 6.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	OTO-104

Reporting group description:

dexamethasone suspension in a solution of poloxamer 407

Serious adverse events	OTO-104		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 142 (2.82%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive ductal breast carcinoma	Additional description: Subject was diagnosed with invasive ductal breast carcinoma on Day 85. The event was considered not related to study drug was ongoing at the date of last contact.		
subjects affected / exposed	1 / 142 (0.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatic carcinoma	Additional description: Subject as diagnosed with pancreatic carcinoma on Day 54. Treatment included surgery, which was planned, not yet performed at the date of last contact. The event was considered not related to study drug.		
subjects affected / exposed	1 / 142 (0.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia	Additional description: Subject had anemia on Day 1. The subject was hospitalized and received blood transfusions from Day 22 to Day 27, when the event was considered resolved and the subject was discharged.		
subjects affected / exposed	1 / 142 (0.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain upper	Additional description: Subject had 3 Serious adverse events: abdominal pain upper, constipation, and helicobacter infection on Day 34. Treatment included lansoprazole, clarithromycin, metronidazole, and Laxido sachets. The event		

	resolved 4 days later.		
subjects affected / exposed	1 / 142 (0.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation	Additional description: Subject had 3 Serious adverse events: abdominal pain upper, constipation, and helicobacter infection on Day 34. Treatment included lansoprazole, clarithromycin, metronidazole, and Laxido sachets. The event resolved 4 days later.		
subjects affected / exposed	1 / 142 (0.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Helicobacter infection	Additional description: Subject had 3 Serious adverse events: abdominal pain upper, constipation, and helicobacter infection on Day 34. Treatment included lansoprazole, clarithromycin, metronidazole, and Laxido sachets. The event resolved 4 days later.		
subjects affected / exposed	1 / 142 (0.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	OTO-104		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 142 (26.06%)		
Injury, poisoning and procedural complications			
Procedural dizziness			
subjects affected / exposed	3 / 142 (2.11%)		
occurrences (all)	3		
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 142 (2.82%)		
occurrences (all)	4		
Dizziness			
subjects affected / exposed	3 / 142 (2.11%)		
occurrences (all)	3		
General disorders and administration site conditions			
Injection site discomfort			
subjects affected / exposed	3 / 142 (2.11%)		
occurrences (all)	3		

Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all) Vertigo subjects affected / exposed occurrences (all) Meniere's disease subjects affected / exposed occurrences (all)	 5 / 142 (3.52%) 5 4 / 142 (2.82%) 4 3 / 142 (2.11%) 3		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	 3 / 142 (2.11%) 3		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	 3 / 142 (2.11%) 3		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	 3 / 142 (2.11%) 3 3 / 142 (2.11%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 April 2016	- Added EudraCT number to title page - Removed telephone as a method to report SAEs. - Added safety fax number as a back-up contact method for reporting SAEs.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported