Clinical trial results:
A randomized, double-blind, placebo-controlled, parallel group study to determine the efficacy, the duration of action, and safety of latanoprost in patients with Menière's disease

Summary

EudraCT number	2013-002261-18
Trial protocol	SE
Global end of trial date	28 April 2016

Results information

Result version number	v1 (current)
This version publication date	19 May 2017
First version publication date	19 May 2017

Trial information

Trial identification

Sponsor protocol code	M05-2013

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01973114
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Synphora AB
Sponsor organisation address	c/o Kajsa Lönroth Brotorpsvägen 11, Sundbyberg, Sweden, 174 41
Public contact	Chief Executive Officer, Synphora AB, +46 703253847, fredrik.henell@synphora.com
Scientific contact	Chief Executive Officer, Synphora AB, +46 703253847, fredrik.henell@synphora.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	23 June 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 April 2016
Global end of trial reached?	Yes
Global end of trial date	28 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to determine the efficacy and duration of action of latanoprost as treatment of Menière's disease

Protection of trial subjects:

Patients were observered in the clinics during the study visits. Physical examination was performed at screening. Vital signs were taken at screening, baseline and end of study. Adverse events were registered from baseline until the last visit. Concomitant medications were collected and reviewed throughout the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 August 2013
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	Sweden: 100
Worldwide total number of subjects	100
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)	73
From 65 to 84 years	27
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited at 12 centers across Sweden. Patients with definite unilateral Menière's disease with an active vertigo component were included in the study. First patient in was 16 October 2013 and last patient last visit was 28 April 2016.

Pre-assignment

Screening details:

The study population was adults aged 18 or above with definite unilateral Menière's disease. Patients had to have a reduction in hearing. Furthermore patients had to have experience of vertigo attacks and tinnitus during the last three months.
A 4-6 weeks run-in period was used in order to obtain accurate baseline values.

Pre-assignment period milestones

Number of subjects started	249[1]
Number of subjects completed	100

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Patient's non-compliance/ protocol violation: 3
Reason: Number of subjects	Protocol deviation: 9
Reason: Number of subjects	Lost to follow-up: 1
Reason: Number of subjects	Inclusion criteria not met: 136

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Denotes the number of patients (249) entering the screening/run-in period.
Of these 249 patients 100 were enrolled/randomized to receive treatment.

Period 1

Period 1 title	Outcome of randomization
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Latanoprost 1 injection

Arm description:

In this arm patients were randomized to one injection of latanoprost.

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

Dosage and administration details:

The study drug contained 0.005% latanoprost (13,14-dihydro-17-phenyl-18,19,20-trinor-PGF2α-isopropyl ester) dissolved in phosphate buffered saline. The dose was 0.4-1.0 ml.

Arm title	Placebo 1 injection

Arm description:

In this arm patients were randomized to one injection of placebo.

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:

The placebo consisted of phosphate buffered saline.
The dose was 0.4-1.0 ml.

Arm title	Latanoprost 3 injections

Arm description:

In this arm patients were randomized to three injections of latanoprost.

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

Dosage and administration details:

The study drug contained 0.005% latanoprost (13,14-dihydro-17-phenyl-18,19,20-trinor-PGF2α-isopropyl ester) dissolved in phosphate buffered saline. The daily dose was 0.4-1.0 ml.

Arm title	Placebo 3 injections

Arm description:

In this arm patients were randomized to three injections of placebo.

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:

The placebo consisted of phosphate buffered saline.
The daily dose was 0.4-1.0 ml.

Number of subjects in period 1	Latanoprost 1 injection	Placebo 1 injection	Latanoprost 3 injections
Started	24	12	42
Completed	24	12	42

Number of subjects in period 1	Placebo 3 injections
Started	22
Completed	22

Period 2

Period 2 title	Treatment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Latanoprost 1 injection

Arm description:

In this arm patients were randomized to one injection of latanoprost.

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

Dosage and administration details:

The study drug contained 0.005% latanoprost (13,14-dihydro-17-phenyl-18,19,20-trinor-PGF2α-isopropyl ester) dissolved in phosphate buffered saline. The dose was 0.4-1.0 ml.

Arm title	Placebo 1 injection

Arm description:

In this arm patients were randomized to one injection of placebo.

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:

The placebo consisted of phosphate buffered saline.
The dose was 0.4-1.0 ml.

Arm title	Latanoprost 3 injections

Arm description:

In this arm patients were randomized to three injections of latanoprost.

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

Dosage and administration details:

The study drug contained 0.005% latanoprost (13,14-dihydro-17-phenyl-18,19,20-trinor-PGF2α-isopropyl ester) dissolved in phosphate buffered saline. The daily dose was 0.4-1.0 ml.

Arm title	Placebo 3 injections

Arm description:

In this arm patients were randomized to three injections of placebo.

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:

The placebo consisted of phosphate buffered saline.
The daily dose was 0.4-1.0 ml.

Number of subjects in period 2	Latanoprost 1 injection	Placebo 1 injection	Latanoprost 3 injections
Started	24	12	42
Completed	20	11	41
Not completed	4	1	1
Consent withdrawn by subject	2	-	-
Plastic ear tube inserted	-	-	1
Wrong intervals	2	-	-
Adverse event, non-fatal	-	1	-
investigator:s failure	-	-	-

Number of subjects in period 2	Placebo 3 injections
Started	22
Completed	21
Not completed	1
Consent withdrawn by subject	-
Plastic ear tube inserted	-
Wrong intervals	-
Adverse event, non-fatal	-
investigator:s failure	1

Baseline characteristics

Reporting groups	
Reporting group title	Latanoprost 1 injection
Reporting group description:	
In this arm patients were randomized to one injection of latanoprost.	
Reporting group title	Placebo 1 injection
Reporting group description:	
In this arm patients were randomized to one injection of placebo.	
Reporting group title	Latanoprost 3 injections
Reporting group description:	
In this arm patients were randomized to three injections of latanoprost.	
Reporting group title	Placebo 3 injections
Reporting group description:	
In this arm patients were randomized to three injections of placebo.	

Reporting group values	Latanoprost 1 injection	Placebo 1 injection	Latanoprost 3 injections
Number of subjects	24	12	42
Age categorical			
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)	18	11	27
From 65-84 years	6	1	15
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	58.4	47.9	59.2
standard deviation	± 7.72	± 13.28	± 12.61
Gender categorical			
Units: Subjects			
Female	9	4	14
Male	15	8	28

Reporting group values	Placebo 3 injections	Total	
Number of subjects	22	100	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	

Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	17	73	
From 65-84 years	5	27	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	53.5		
standard deviation	± 13.05	-	
Gender categorical			
Units: Subjects			
Female	11	38	
Male	11	62	

Subject analysis sets

Subject analysis set title	Latanoprost 1 or 3 injections
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients receiving 1 injection of Latanoprost or 3 injections of Latanoprost	
Subject analysis set title	Placebo 1 or 3 injections
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients receiving 1 injection of Placebo or 3 injections of Placebo	

Reporting group values	Latanoprost 1 or 3 injections	Placebo 1 or 3 injections	
Number of subjects	66	34	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	45	28	
From 65-84 years	21	6	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	58.9	51.5	
standard deviation	± 11.02	± 13.21	
Gender categorical			
Units: Subjects			
Female	23	15	
Male	43	19	

End points

End points reporting groups

Reporting group title	Latanoprost 1 injection
Reporting group description:	
In this arm patients were randomized to one injection of latanoprost.	
Reporting group title	Placebo 1 injection
Reporting group description:	
In this arm patients were randomized to one injection of placebo.	

Reporting group title	Latanoprost 3 injections
Reporting group description:	
In this arm patients were randomized to three injections of latanoprost.	
Reporting group title	Placebo 3 injections
Reporting group description:	
In this arm patients were randomized to three injections of placebo.	

Reporting group title	Latanoprost 1 injection
Reporting group description:	
In this arm patients were randomized to one injection of latanoprost.	
Reporting group title	Placebo 1 injection
Reporting group description:	
In this arm patients were randomized to one injection of placebo.	

Reporting group title	Latanoprost 3 injections
Reporting group description:	
In this arm patients were randomized to three injections of latanoprost.	
Reporting group title	Placebo 3 injections
Reporting group description:	
In this arm patients were randomized to three injections of placebo.	

Subject analysis set title	Latanoprost 1 or 3 injections
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients receiving 1 injection of Latanoprost or 3 injections of Latanoprost	
Subject analysis set title	Placebo 1 or 3 injections
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients receiving 1 injection of Placebo or 3 injections of Placebo	

Primary: Speech discrimination in noise Visit 3

End point title	Speech discrimination in noise Visit 3
End point description:	
Change in speech discrimination in noise (ISO 8253-3) from Baseline (Day 1) to Day 14. At Baseline (Visit 2a/Day 1) speech discrimination in noise was measured (50 Swedish PB words) using a speech weighted noise, S/N = 4, where the signal is adjusted to each patient's most comfortable level. This signal level is to be applied at all subsequent measurements. The endpoint is measured in percentage (%). A positive score in change from baseline means an improvement in hearing.	

End point type	Primary
End point timeframe:	
Day 14 compared to Baseline (Day 1)	

End point values	Latanoprost 1 or 3 injections	Placebo 1 or 3 injections		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	66	34		
Units: percentage				
arithmetic mean (standard deviation)	2.7 (± 13.94)	1.4 (± 12.12)		

Statistical analyses

Statistical analysis title	Change in speech discrimination in noise

Statistical analysis description:

Change in speech discrimination in noise from baseline (Day 1) to Day 14.
A positive score in change from baseline means an improvement in hearing.

Comparison groups	Latanoprost 1 or 3 injections v Placebo 1 or 3 injections
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.8829
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.363
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.524
upper limit	5.25

Notes:

[1] - The analysis performs a weighted comparison of Latanoprost 1 injection and Latanoprost 3 injections compared to Placebo 1 injection and Placebo 3 injections. The weight are proportional to the number patients in the respective group at Day 14.

Secondary: Speech discrimination in noise Visit 4

End point title	Speech discrimination in noise Visit 4

End point description:

End point type	Secondary

End point timeframe:

Day 28 compared to Baseline (Day 1)

End point values	Latanoprost 1 or 3 injections	Placebo 1 or 3 injections		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	59	33		
Units: percentage				
arithmetic mean (standard deviation)	1.8 (± 17.38)	5.21 (± 12.34)		

Statistical analyses

Statistical analysis title	Change in speech discrimination in noise
Statistical analysis description:	
Change in speech discrimination in noise from baseline (Day 1) to Day 28. A positive score in change from baseline means an improvement in hearing.	
Comparison groups	Latanoprost 1 or 3 injections v Placebo 1 or 3 injections
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2652
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.446
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.562
upper limit	2.669

Secondary: Speech discrimination in noise Visit 5

End point title	Speech discrimination in noise Visit 5
End point description:	
A positive score in change from baseline means an improvement in hearing.	
End point type	Secondary
End point timeframe:	
Day 42 compared to Baseline (Day 1)	

End point values	Latanoprost 1 or 3 injections	Placebo 1 or 3 injections		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	62	29		
Units: percentage				
arithmetic mean (standard deviation)	4.21 (± 18.92)	6.48 (± 12.59)		

Statistical analyses

Statistical analysis title	Change in speech discrimination in noise

Statistical analysis description:

Change in speech discrimination in noise from baseline (Day 1) to Day 42.
A positive score in change from baseline means an improvement in hearing.

Comparison groups	Latanoprost 1 or 3 injections v Placebo 1 or 3 injections
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.3547
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.106
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.75
upper limit	3.538

Notes:

[2] - The analysis performs a weighted comparison of Latanoprost 1 injection and Latanoprost 3 injections compared to Placebo 1 injection and Placebo 3 injections. The weight are proportional to the number patients in the respective group at Day 14

Secondary: Speech discrimination in noise Visit 6

End point title	Speech discrimination in noise Visit 6

End point description:

A positive score in change from baseline means an improvement in hearing.

End point type	Secondary

End point timeframe:

Day 56 compared to Baseline (Day 1)

End point values	Latanoprost 1 or 3 injections	Placebo 1 or 3 injections		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	31		
Units: percentage				
arithmetic mean (standard deviation)	3.02 (± 17.52)	7.45 (± 13.57)		

Statistical analyses

Statistical analysis title	Change in speech discrimination in noise

Statistical analysis description:

Change in speech discrimination in noise from baseline (Day 1) to Day 56.
A positive score in change from baseline means an improvement in hearing.

Comparison groups	Latanoprost 1 or 3 injections v Placebo 1 or 3 injections

Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.1423
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-5.025
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.77
upper limit	1.724

Notes:

[3] - The analysis performs a weighted comparison of Latanoprost 1 injection and Latanoprost 3 injections compared to Placebo 1 injection and Placebo 3 injections. The weight are proportional to the number patients in the respective group at Day 14

Secondary: Speech discrimination in noise Visit 7

End point title	Speech discrimination in noise Visit 7

End point description:

A positive score in change from baseline means an improvement in hearing.

End point type	Secondary

End point timeframe:

Day 84 compared to Baseline (Day 1)

End point values	Latanoprost 1 or 3 injections	Placebo 1 or 3 injections		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	63	33		
Units: percentage				
arithmetic mean (standard deviation)	4.84 (± 21.05)	9.67 (± 13.23)		

Statistical analyses

Statistical analysis title	Change in speech discrimination in noise

Statistical analysis description:

Change in speech discrimination in noise from baseline (Day 1) to Day 84.
A positive score in change from baseline means an improvement in hearing.

Comparison groups	Latanoprost 1 or 3 injections v Placebo 1 or 3 injections
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.1369
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-5.442

Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.65
upper limit	1.766

Notes:

[4] - The analysis performs a weighted comparison of Latanoprost 1 injection and Latanoprost 3 injections compared to Placebo 1 injection and Placebo 3 injections. The weight are proportional to the number patients in the respective group at Day 14

Secondary: Tinnitus (THI score) Visit 3

End point title	Tinnitus (THI score) Visit 3

End point description:

A negative score in change from baseline means an improvement.

End point type	Secondary

End point timeframe:

Day 14 compared to Baseline (Day 1)

End point values	Latanoprost 1 or 3 injections	Placebo 1 or 3 injections		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	66	34		
Units: score				
arithmetic mean (standard deviation)	-3.67 (± 8.79)	-2.18 (± 9.26)		

Statistical analyses

Statistical analysis title	Change in Tinnitus (THI score)

Statistical analysis description:

Change in Tinnitus (THI score) Day 14 compared to baseline (Day 1).
A negative score in change from baseline means an improvement.

Comparison groups	Placebo 1 or 3 injections v Latanoprost 1 or 3 injections
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.3857
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.646
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.399
upper limit	2.107

Notes:

[5] - The analysis performs a weighted comparison of Latanoprost 1 injection and Latanoprost 3 injections compared to Placebo 1 injection and Placebo 3 injections. The weight are proportional to the number patients in the respective group at Day 14

Secondary: Tinnitus (THI score) Visit 4

End point title	Tinnitus (THI score) Visit 4

End point description:

A negative score in change from baseline means an improvement.

End point type	Secondary

End point timeframe:

Day 28 compared to Baseline (Day 1)

End point values	Latanoprost 1 or 3 injections	Placebo 1 or 3 injections		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	61	33		
Units: score				
arithmetic mean (standard deviation)	-4.69 (± 10.78)	-4.61 (± 13.84)		

Statistical analyses

Statistical analysis title	Change in Tinnitus (THI score)

Statistical analysis description:

Change in Tinnitus (THI score) Day 14 compared to baseline (Day 1).
A negative score in change from baseline means an improvement.

Comparison groups	Latanoprost 1 or 3 injections v Placebo 1 or 3 injections
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.9753
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.223
upper limit	5.063

Notes:

[6] - The analysis performs a weighted comparison of Latanoprost 1 injection and Latanoprost 3 injections compared to Placebo 1 injection and Placebo 3 injections. The weight are proportional to the number patients in the respective group at Day 14

Secondary: Tinnitus (THI score) Visit 5

End point title	Tinnitus (THI score) Visit 5

End point description:

A negative score in change from baseline means an improvement.

End point type	Secondary

End point timeframe:

Day 42 compared to Baseline (Day 1)

End point values	Latanoprost 1 or 3 injections	Placebo 1 or 3 injections		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	61	30		
Units: score				
arithmetic mean (standard deviation)	-6.26 (± 11.5)	-5.53 (± 16.19)		

Statistical analyses

Statistical analysis title	Change in Tinnitus (THI score)

Statistical analysis description:

Change in Tinnitus (THI score) Day 14 compared to baseline (Day 1).
A negative score in change from baseline means an improvement.

Comparison groups	Latanoprost 1 or 3 injections v Placebo 1 or 3 injections
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.7121
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.082
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.897
upper limit	4.734

Notes:

[7] - The analysis performs a weighted comparison of Latanoprost 1 injection and Latanoprost 3 injections compared to Placebo 1 injection and Placebo 3 injections. The weight are proportional to the number patients in the respective group at Day 14

Secondary: Tinnitus (THI score) Visit 6

End point title	Tinnitus (THI score) Visit 6

End point description:

A negative score in change from baseline means an improvement.

End point type	Secondary

End point timeframe:

Day 56 compared to Baseline (Day 1)

End point values	Latanoprost 1 or 3 injections	Placebo 1 or 3 injections		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	62	32		
Units: score				
arithmetic mean (standard deviation)	-7.03 (± 12.39)	-4.5 (± 15.97)		

Statistical analyses

Statistical analysis title	Change in Tinnitus (THI score)

Statistical analysis description:

Change in Tinnitus (THI score) Day 14 compared to baseline (Day 1).
A negative score in change from baseline means an improvement.

Comparison groups	Latanoprost 1 or 3 injections v Placebo 1 or 3 injections
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.3632
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.48
upper limit	3.14

Notes:

[8] - The analysis performs a weighted comparison of Latanoprost 1 injection and Latanoprost 3 injections compared to Placebo 1 injection and Placebo 3 injections. The weight are proportional to the number patients in the respective group at Day 14

Secondary: Tinnitus (THI score) Visit 7

End point title	Tinnitus (THI score) Visit 7

End point description:

A negative score in change from baseline means an improvement.

End point type	Secondary

End point timeframe:

Day 84 compared to Baseline (Day 1)

End point values	Latanoprost 1 or 3 injections	Placebo 1 or 3 injections		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	63	33		
Units: score				
arithmetic mean (standard deviation)	-6.67 (± 14.89)	-4.67 (± 16.36)		

Statistical analyses

Statistical analysis title	Change in Tinnitus (THI score)
Statistical analysis description:	
Change in Tinnitus (THI score) Day 14 compared to baseline (Day 1). A negative score in change from baseline means an improvement.	
Comparison groups	Latanoprost 1 or 3 injections v Placebo 1 or 3 injections
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.5026
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.235
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.84
upper limit	4.37

Notes:

[9] - The analysis performs a weighted comparison of Latanoprost 1 injection and Latanoprost 3 injections compared to Placebo 1 injection and Placebo 3 injections. The weight are proportional to the number patients in the respective group at Day 14

Secondary: Proportion of days with vertigo attacks Week 0-4

End point title	Proportion of days with vertigo attacks Week 0-4
End point description:	
A negative score means an improvement, i.e. fewer days virtigo.	
End point type	Secondary
End point timeframe:	
Week 0-4 compared to run-in period (last 4 weeks prior to treatment)	

End point values	Latanoprost 1 or 3 injections	Placebo 1 or 3 injections		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	66	34		
Units: percentage				
arithmetic mean (standard deviation)	-1.8 (± 10.37)	-4 (± 14.36)		

Statistical analyses

Statistical analysis title	Change in proportion of days with vertigo attacks

Statistical analysis description:

Change in proportion of days with vertigo attacks Week 0-4 compared to run-in period (last 4 weeks prior to treatment).
A negative score means an improvement, i.e. fewer days virtigo.

Comparison groups	Latanoprost 1 or 3 injections v Placebo 1 or 3 injections
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3764
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	2.145
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.651
upper limit	6.941

Secondary: Proportion of days with vertigo attacks Week 4-8

End point title	Proportion of days with vertigo attacks Week 4-8

End point description:

A negative score means an improvement, i.e. fewer days virtigo.

End point type	Secondary

End point timeframe:

Week 4-8 compared to run-in period (last 4 weeks prior to treatment)

End point values	Latanoprost 1 or 3 injections	Placebo 1 or 3 injections		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	66	34		
Units: percentage				
arithmetic mean (standard deviation)	-2.56 (± 11.45)	-5.79 (± 16.24)		

Statistical analyses

Statistical analysis title	Change in proportion of days with vertigo attacks

Statistical analysis description:

Change in proportion of days with vertigo attacks Week 4-8 compared to run-in period (last 4 weeks prior to treatment).
A negative score means an improvement, i.e. fewer days virtigo.

Comparison groups	Latanoprost 1 or 3 injections v Placebo 1 or 3 injections

Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.2336
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	3.229
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.123
upper limit	8.582

Notes:

[10] - The analysis performs a weighted comparison of Latanoprost 1 injection and Latanoprost 3 injections compared to Placebo 1 injection and Placebo 3 injections. The weight are proportional to the number patients in the respective group at Day 14

Secondary: Proportion of days with vertigo attacks Week 8-12

End point title	Proportion of days with vertigo attacks Week 8-12

End point description:

A negative score means an improvement, i.e. fewer days virtigo.

End point type	Secondary

End point timeframe:

Week 8-12 compared to run-in period (last 4 weeks prior to treatment)

End point values	Latanoprost 1 or 3 injections	Placebo 1 or 3 injections		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	66	33		
Units: percentage				
arithmetic mean (standard deviation)	-5.7 (± 13.47)	-7.8 (± 15.71)		

Statistical analyses

Statistical analysis title	Change in proportion of days with vertigo attacks

Statistical analysis description:

Change in proportion of days with vertigo attacks Week 8-12 compared to run-in period (last 4 weeks prior to treatment).
A negative score means an improvement, i.e. fewer days virtigo.

Comparison groups	Latanoprost 1 or 3 injections v Placebo 1 or 3 injections
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.5328
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.807

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.932
upper limit	7.546

Notes:

[11] - The analysis performs a weighted comparison of Latanoprost 1 injection and Latanoprost 3 injections compared to Placebo 1 injection and Placebo 3 injections. The weight are proportional to the number patients in the respective group at Day 14

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded from baseline (Day 1) until last the last visit for each subject.

Adverse event reporting additional description:

All adverse events, whether volunteered by the subject, discovered by Investigator questioning, or detected through physical examination, laboratory test or other means was documented.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	Latanoprost 1 injection

Reporting group description:

In this arm patients were randomized to one injection of latanoprost.

Reporting group title	Placebo 1 injection

Reporting group description:

In this arm patients were randomized to one injection of placebo.
The placebo consisted of phosphate buffered saline.

Reporting group title	Latanoprost 3 injections

Reporting group description:

In this arm patients were randomized to three injections of latanoprost.

Reporting group title	Placebo 3 injections

Reporting group description:

In this arm patients were randomized to three injections of placebo.
The placebo consisted of phosphate buffered saline.

Serious adverse events	Latanoprost 1 injection	Placebo 1 injection	Latanoprost 3 injections
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 42 (2.38%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo 3 injections		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 22 (0.00%)		
number of deaths (all causes)	0		

number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Latanoprost 1 injection	Placebo 1 injection	Latanoprost 3 injections
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 24 (25.00%)	5 / 12 (41.67%)	23 / 42 (54.76%)
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 12 (8.33%)	1 / 42 (2.38%)
occurrences (all)	0	1	1
Fatigue			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	2 / 42 (4.76%)
occurrences (all)	0	0	2
Infusion related reaction			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 24 (0.00%)	1 / 12 (8.33%)	0 / 42 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Psychiatric disorders			

Insomnia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Depression			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Auricular haematoma			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Radius fracture			
subjects affected / exposed	0 / 24 (0.00%)	1 / 12 (8.33%)	0 / 42 (0.00%)
occurrences (all)	0	1	0
Procedural headache			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 24 (4.17%)	3 / 12 (25.00%)	10 / 42 (23.81%)
occurrences (all)	1	5	41
Dizziness			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	2 / 42 (4.76%)
occurrences (all)	0	0	4
Visual field defect			
subjects affected / exposed	0 / 24 (0.00%)	1 / 12 (8.33%)	0 / 42 (0.00%)
occurrences (all)	0	1	0
Tremor			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Ear pain			

subjects affected / exposed	2 / 24 (8.33%)	0 / 12 (0.00%)	2 / 42 (4.76%)
occurrences (all)	14	0	3
Hyperacusis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Vertigo			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Ear discomfort			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Tinnitus			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Eye swelling			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Abdominal pain upper			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Dental discomfort			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 24 (0.00%)	1 / 12 (8.33%)	1 / 42 (2.38%)
occurrences (all)	0	1	2

Arthralgia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Neck pain			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 24 (8.33%)	1 / 12 (8.33%)	3 / 42 (7.14%)
occurrences (all)	3	1	3
Ear infection			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	3 / 42 (7.14%)
occurrences (all)	0	0	3
Sinusitis			
subjects affected / exposed	0 / 24 (0.00%)	1 / 12 (8.33%)	1 / 42 (2.38%)
occurrences (all)	0	1	1
Otitis externa			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	0 / 42 (0.00%)
occurrences (all)	1	0	0
Viral infection			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Oral herpes			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	0 / 42 (0.00%)
occurrences (all)	1	0	0
Otitis media			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Diverticulitis			
subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	0 / 42 (0.00%)
occurrences (all)	1	0	0
Otitis media acute			

subjects affected / exposed	1 / 24 (4.17%)	0 / 12 (0.00%)	0 / 42 (0.00%)
occurrences (all)	1	0	0
Injection site pain			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Thirst			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Application site pain			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Pain			
subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1

Non-serious adverse events	Placebo 3 injections		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 22 (40.91%)		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Infusion related reaction			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	2		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	2		

Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Depression			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Auricular haematoma			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Radius fracture			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Procedural headache			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Dizziness			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Visual field defect			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Tremor			

subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Hyperacusis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Vertigo			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Ear discomfort			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Tinnitus			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Eye disorders			
Eye swelling			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	2		
Dental discomfort			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue			

disorders			
Back pain			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Arthralgia			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Neck pain			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Ear infection			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Otitis externa			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Viral infection			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Oral herpes			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Otitis media			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Gastroenteritis			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Diverticulitis			

subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Otitis media acute			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Injection site pain			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Thirst			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Application site pain			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Pain			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported