Clinical trial results:
Therapeutic Equivalence (non-inferiority), Randomized, Observer-blind, two Parallel Group, Clinical Trial for Comparing the Efficacy and Tolerability of a new Generic Preservative-Free Formulation of Latanoprost 50g/ml/Timolol 5mg/ml Eye Drops vs Xalacom® Eye Drops in Patients with Open Angle Glaucoma, or Ocular Hypertension.

Summary

EudraCT number	2017-004524-29
Trial protocol	GR
Global end of trial date	17 December 2018

Results information

Result version number	v1 (current)
This version publication date	31 March 2019
First version publication date	31 March 2019

Trial information

Trial identification

Sponsor protocol code	BECRO/PHN/LATIM

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Pharmathen S.A.
Sponsor organisation address	6 Dervenakion Str, Pallini Attica, Greece, 15351
Public contact	Lida Kalantzi, PhD Head of Scientific Affairs, Pharmathen S.A. , +30 2106604300, lkalantzi@pharmathen.com
Scientific contact	Lida Kalantzi, PhD Head of Scientific Affairs, Pharmathen S.A. , +30 2106604300, lkalantzi@pharmathen.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	24 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 December 2018
Global end of trial reached?	Yes
Global end of trial date	17 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To confirm the clinical non-inferiority of a generic ophthalmic product of Latanoprost 50µg/ml/Timolol 5mg/ml fixed combination which is preservative-free (test) compared with the marketed preservative-containing Xalacom® (reference) eye drops in patients with open angle glaucoma or ocular hypertension by examining the change of IOP at 8:00am from end of study to baseline.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial participants were followed.

Background therapy:

-

Evidence for comparator:

-

Actual start date of recruitment	29 June 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	Greece: 210
Worldwide total number of subjects	210
EEA total number of subjects	210

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)	53

From 65 to 84 years	145
85 years and over	12

Subject disposition

Recruitment

Recruitment details:

Study sites: Ophthalmiatreio Athens, General Hospital of Larissa, General University Hospital of Athens Attikon, General University Hospital of Thessaloniki AXEPA, IASO
Thessalias, General University Hospital of Patra, General Hospital of Thessaloniki Ippokrateio, NIMITS 417

Pre-assignment

Screening details:

This study was conducted in 8 clinical sites in Greece between June 29, 2018 and December 17,2018.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Investigator[1]

Blinding implementation details:

Observer-blind

Arms

Are arms mutually exclusive?	Yes
Arm title	Test

Arm description:

Latanoprost 50 µg/ml + Timolol 5mg/ml eye drops solution Preservative free

Arm type	Test
Investigational medicinal product name	Latanoprost 50 µg/ml + Timolol 5mg/ml eye drops solution Preservative free
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

One drop of the Test product containing Latanoprost 50µg/ml and Timolol 5mg/ml fixed combination preservative-free in each eye once daily in the evening (approximately at 20:00 pm).

Arm title	Reference

Arm description:

XALACOM®

Arm type	Active comparator
Investigational medicinal product name	Xalacom®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

One drop of XALACOM® containing Latanoprost 50µg/ml and Timolol 5mg/ml in each eye once daily in the evening (approximately at 20:00 pm).

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Due to differences in the packaging of the study medication, the investigator measuring IOP was masked to study medication.

Number of subjects in period 1	Test	Reference
Started	106	104
Completed	96	100
Not completed	10	4
Consent withdrawn by subject	3	1
Adverse event, non-fatal	2	-
Protocol deviation	5	3

Baseline characteristics

Reporting groups	
Reporting group title	Test
Reporting group description:	
Latanoprost 50 µg/ml + Timolol 5mg/ml eye drops solution Preservative free	
Reporting group title	Reference
Reporting group description:	
XALACOM®	

Reporting group values	Test	Reference	Total
Number of subjects	106	104	210
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	69.88	70.80	
standard deviation	± 11.46	± 11.12	-
Gender categorical Units: Subjects			
Female	57	51	108
Male	49	53	102

Subject analysis sets	
Subject analysis set title	PP
Subject analysis set type	Per protocol

Subject analysis set description:

The per protocol (PP) population includes all those of the ITT population who had no major protocol deviations, who completed IOP measurements within the allowed time frames, who completed at least 12 weeks of treatment with the last dose administered before the 12-week visit, and who did not take prohibited concurrent medication.

Reporting group values	PP		
Number of subjects	196		
Age categorical Units: Subjects			
In utero			

Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	70.22		
standard deviation	± 11.34		
Gender categorical Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	Test
Reporting group description:	
Latanoprost 50 µg/ml + Timolol 5mg/ml eye drops solution Preservative free	
Reporting group title	Reference
Reporting group description:	
XALACOM®	
Subject analysis set title	PP
Subject analysis set type	Per protocol
Subject analysis set description:	
The per protocol (PP) population includes all those of the ITT population who had no major protocol deviations, who completed IOP measurements within the allowed time frames, who completed at least 12 weeks of treatment with the last dose administered before the 12-week visit, and who did not take prohibited concurrent medication.	

Primary: Change in IOP at 8:00am in study eye from end of treatment (week 12) to baseline (week 0)

End point title	Change in IOP at 8:00am in study eye from end of treatment (week 12) to baseline (week 0)
End point description:	
The change in IOP at 8:00 am in study eye from end of treatment (week 12) to baseline (week 0)	
End point type	Primary
End point timeframe:	
End of treatment (week 12) to baseline (week 0)	

End point values	Test	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	100		
Units: mm Hg				
arithmetic mean (confidence interval 95%)	-7.965 (-8.476 to -7.454)	-8.589 (-9.089 to -8.088)		

Statistical analyses

Statistical analysis title	IOP change
Statistical analysis description:	
The analysis of covariance (ANCOVA) model was used to analyse the change in IOP with baseline IOP as the covariate, and treatment as a factor. The treatment difference and a two-sided 95% confidence interval (CI) for the difference were calculated. The preservative-free latanoprost/timolol eye drops (Test) was considered to be non-inferior to the marketed Xalacom® including preservative (Reference), if the upper limit of the 95% CI of the difference was < 1.5 mmHg	
Comparison groups	Test v Reference

Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Mean difference (final values)
Point estimate	0.624
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.094
upper limit	1.341
Variability estimate	Standard error of the mean
Dispersion value	0.364

Notes:

[1] - Non-inferiority

Secondary: Change in IOP at 12:00 pm from 12 weeks to baseline

End point title	Change in IOP at 12:00 pm from 12 weeks to baseline

End point description:

The change in IOP at 12:00 am in study eye from end of treatment (week 12) to baseline (week 0) in subjects treated with the test product as compared to subjects treated with the reference product

End point type	Secondary

End point timeframe:

End of treatment (week 12) to baseline (week 0)

End point values	Test	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	100		
Units: mm Hg				
arithmetic mean (confidence interval 95%)	-8.13 (-8.597 to -7.663)	-8.7 (-9.157 to -8.242)		

Statistical analyses

Statistical analysis title	IOP change at 12:00 pm from 12 weeks to baseline

Statistical analysis description:

The secondary endpoint "change in IOP at 12:00 pm from weeks 12 to baseline" was analysed using an ANCOVA model with the respective baseline IOP as the covariate, and treatment as a factor

Comparison groups	Test v Reference
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Mean difference (final values)
Point estimate	0.569

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.086
upper limit	1.225
Variability estimate	Standard error of the mean
Dispersion value	0.332

Secondary: IOP change at 16:00 pm from 12 weeks to baseline

End point title	IOP change at 16:00 pm from 12 weeks to baseline

End point description:

The change in IOP at 16:00 pm in study eye from end of treatment (week 12) to baseline (week 0) in subjects treated with the test product as compared to subjects treated with the reference product

End point type	Secondary

End point timeframe:

End of treatment (week 12) to baseline (week 0)

End point values	Test	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	100		
Units: mm Hg				
arithmetic mean (confidence interval 95%)	-8.177 (-8.676 to -7.677)	-8.482 (-8.969 to -7.996)		

Statistical analyses

Statistical analysis title	IOP change at 16:00 pm from 12 weeks to baseline

Statistical analysis description:

The scondary endpoint "change in IOP at 16:00 pm from weeks 12 to baseline" was analysed using an ANCOVA model with the respective baseline IOP as the covariate and treatment as a factor

Comparison groups	Test v Reference
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	Mean difference (final values)
Point estimate	0.306
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.392
upper limit	1.003
Variability estimate	Standard error of the mean
Dispersion value	0.354

Notes:

[2] - Non-inferiority

Secondary: Change in IOP at 8:00 am in study eye from 6 weeks to baseline

End point title	Change in IOP at 8:00 am in study eye from 6 weeks to baseline

End point description:

Change in IOP at 8:00 am in study eye from week 6 to baseline (week 0) in subjects treated with the test product as compared to subjects treated with the reference product

End point type	Secondary

End point timeframe:

From week 6 to baseline (week 0)

End point values	Test	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	100		
Units: mm Hg				
arithmetic mean (confidence interval 95%)	-7.732 (-8.230 to -7.233)	-8.243 (-8.731 to -7.754)		

Statistical analyses

Statistical analysis title	Change in IOP at 8:00 am from 6 weeks to baseline

Statistical analysis description:

The secondary endpoint "change in IOP at 8:00 am from weeks 6 to baseline" was analysed using an ANCOVA model with the respective baseline IOP as the covariate and treatment as a factor

Comparison groups	Test v Reference
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Mean difference (final values)
Point estimate	0.511
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.188
upper limit	1.21
Variability estimate	Standard error of the mean
Dispersion value	0.355

Secondary: Change in IOP at 12:00 pm in study eye from 6 weeks to baseline

End point title	Change in IOP at 12:00 pm in study eye from 6 weeks to baseline

End point description:

Change in IOP at 12:00 pm in study eye from week 6 to baseline (week 0) in subjects treated with the test product as compared to subjects treated with the reference product

End point type	Secondary

End point timeframe:

From week 6 to baseline (week 0)

End point values	Test	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	100		
Units: mm Hg				
arithmetic mean (confidence interval 95%)	-7.880 (-8.356 to -7.404)	-8.351 (-8.817 to -7.884)		

Statistical analyses

Statistical analysis title	Change in IOP at 12:00 pm from 6 weeks to baseline

Statistical analysis description:

The secondary endpoint "change in IOP at 8:00 am from weeks 6 to baseline" was analysed using an ANCOVA model with the respective baseline IOP as the covariate and treatment as a factor

Comparison groups	Test v Reference
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Mean difference (final values)
Point estimate	0.471
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.197
upper limit	1.139
Variability estimate	Standard error of the mean
Dispersion value	0.339

Secondary: Change in IOP at 16:00 pm in study eye from 6 weeks to baseline

End point title	Change in IOP at 16:00 pm in study eye from 6 weeks to baseline

End point description:

Change in IOP at 16:00 pm in study eye from week 6 to baseline (week 0) in subjects treated with the test product as compared to subjects treated with the reference product

End point type	Secondary

End point timeframe:

From week 6 to baseline (week 0)

End point values	Test	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	100		
Units: mm Hg				
arithmetic mean (confidence interval 95%)	-7.923 (-8.440 to -7.406)	-8.074 (-8.581 to -7.568)		

Statistical analyses

Statistical analysis title	Change in IOP at 16:00 pm from 6 weeks to baseline
Statistical analysis description:	
The secondary endpoint "change in IOP at 16:00 pm from 6 weeks to baseline" was analysed using an ANCOVA model with the respective baseline IOP as the covariate and treatment as a factor	
Comparison groups	Test v Reference
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Mean difference (final values)
Point estimate	0.152
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.572
upper limit	0.875
Variability estimate	Standard error of the mean
Dispersion value	0.367

Secondary: Change in IOP at 8:00 am in study eye from 2 weeks to baseline	
End point title	Change in IOP at 8:00 am in study eye from 2 weeks to baseline
End point description:	
Change in IOP at 8:00 am in study eye from week 2 to baseline (week 0) in subjects treated with the test product as compared to subjects treated with the reference product	
End point type	Secondary
End point timeframe:	
From week 2 to baseline (week 0)	

End point values	Test	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	100		
Units: mm Hg				
arithmetic mean (confidence interval 95%)	-6.887 (-7.413 to -6.362)	-7.008 (-7.523 to -6.493)		

Statistical analyses

Statistical analysis title	Change in IOP at 8:00 am from 2 weeks to baseline

Statistical analysis description:

The secondary endpoint "change in IOP at 8:00 am from 2 weeks to baseline" was analysed using an ANCOVA model with the respective baseline IOP as the covariate and treatment as a factor

Comparison groups	Test v Reference
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Mean difference (final values)
Point estimate	0.121
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.617
upper limit	0.858
Variability estimate	Standard error of the mean
Dispersion value	0.374

Secondary: Change in IOP at 12:00 pm in study eye from 2 weeks to baseline

End point title	Change in IOP at 12:00 pm in study eye from 2 weeks to baseline

End point description:

Change in IOP at 12:00 pm in study eye from week 2 to baseline (week 0) in subjects treated with the test product as compared to subjects treated with the reference product

End point type	Secondary

End point timeframe:

From week 2 to baseline (week 0)

End point values	Test	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	100		
Units: mm Hg				
arithmetic mean (confidence interval 95%)	-7.033 (-7.555 to -6.511)	-6.983 (-7.495 to -6.472)		

Statistical analyses

Statistical analysis title	Change in IOP at 12:00 pm from weeks 2 to baseline
Statistical analysis description:	
The secondary endpoint "change in IOP at 12:00 pm from 2 weeks to baseline" was analysed using an ANCOVA model with the respective baseline IOP as the covariate and treatment as a factor	
Comparison groups	Test v Reference
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.049
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.783
upper limit	0.684
Variability estimate	Standard error of the mean
Dispersion value	0.372

Secondary: Change in IOP at 16:00 pm in study eye from 2 weeks to baseline

End point title	Change in IOP at 16:00 pm in study eye from 2 weeks to baseline
End point description:	
Change in IOP at 16:00 pm in study eye from week 2 to baseline (week 0) in subjects treated with the test product as compared to subjects treated with the reference product	
End point type	Secondary
End point timeframe:	
From week 2 to baseline (week 0)	

End point values	Test	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	100		
Units: mm Hg				
arithmetic mean (confidence interval 95%)	-6.875 (-7.414 to -6.337)	-6.920 (-7.447 to -6.392)		

Statistical analyses

Statistical analysis title	Change in IOP at 16:00 pm from 2 weeks to baseline

Statistical analysis description:

The secondary endpoint "change in IOP at 16:00 pm from 2 weeks to baseline" was analysed using an ANCOVA model with the respective baseline IOP as the covariate and treatment as a factor

Comparison groups	Test v Reference
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Mean difference (final values)
Point estimate	0.044
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.71
upper limit	0.798
Variability estimate	Standard error of the mean
Dispersion value	0.382

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From baseline to end of treatment (12 weeks)	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1
Reporting groups	
Reporting group title	Test
Reporting group description: -	
Reporting group title	Reference
Reporting group description: -	

Serious adverse events	Test	Reference	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 106 (0.00%)	0 / 104 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Test	Reference	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 106 (33.96%)	42 / 104 (40.38%)	
Cardiac disorders			
Heart rate decreased			
subjects affected / exposed	0 / 106 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 106 (0.94%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	2 / 106 (1.89%)	0 / 104 (0.00%)	
occurrences (all)	2	0	
General disorders and administration			

site conditions			
Oedema peripheral (ankle oedema)			
subjects affected / exposed	1 / 106 (0.94%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Blurred vision			
subjects affected / exposed	4 / 106 (3.77%)	4 / 104 (3.85%)	
occurrences (all)	4	7	
Burning sensation			
subjects affected / exposed	1 / 106 (0.94%)	5 / 104 (4.81%)	
occurrences (all)	1	5	
Conjuctival hyperaemia			
subjects affected / exposed	7 / 106 (6.60%)	13 / 104 (12.50%)	
occurrences (all)	7	13	
Diplopia			
subjects affected / exposed	1 / 106 (0.94%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Abnormal sensation in eye			
subjects affected / exposed	0 / 106 (0.00%)	2 / 104 (1.92%)	
occurrences (all)	0	2	
Eye irritation			
subjects affected / exposed	2 / 106 (1.89%)	0 / 104 (0.00%)	
occurrences (all)	2	0	
Irritation during instillation			
subjects affected / exposed	2 / 106 (1.89%)	1 / 104 (0.96%)	
occurrences (all)	2	1	
Ocular hyperaemia (upon waking up)			
subjects affected / exposed	0 / 106 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
Eye pain/Eyelid pain			
subjects affected / exposed	4 / 106 (3.77%)	10 / 104 (9.62%)	
occurrences (all)	4	10	
Foreign body sensation			
subjects affected / exposed	7 / 106 (6.60%)	12 / 104 (11.54%)	
occurrences (all)	7	12	
Instillation site burn			

subjects affected / exposed	0 / 106 (0.00%)	2 / 104 (1.92%)	
occurrences (all)	0	2	
IOP increased			
subjects affected / exposed	13 / 106 (12.26%)	15 / 104 (14.42%)	
occurrences (all)	13	15	
Eye Pruritus/Eyelid Pruritus			
subjects affected / exposed	6 / 106 (5.66%)	2 / 104 (1.92%)	
occurrences (all)	6	2	
Lacrimation increased			
subjects affected / exposed	1 / 106 (0.94%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Visual impairment			
subjects affected / exposed	1 / 106 (0.94%)	1 / 104 (0.96%)	
occurrences (all)	1	1	
Vitreous Floaters			
subjects affected / exposed	1 / 106 (0.94%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Erythema of Eyelid			
subjects affected / exposed	0 / 106 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	

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