Clinical trial results:
A PHASE III, MULTICENTRE, RANDOMISED, INVESTIGATOR-MASKED, CROSSOVER, COMPARATIVE, NON-INFERIORITY TRIAL EVALUATING THE EFFICACY AND TOLERABILITY OF GENERIC LATANOPROST 0.05 MG/ML EYE DROPS SOLUTION (POLPHARMA S.A.) COMPARED TO XALATAN® (LATANOPROST 0.005 % OPHTHALMIC SOLUTION, PFIZER) IN PATIENTS WITH OCULAR HYPERTENSION OR PRIMARY OPEN ANGLE GLAUCOMA.

Summary

EudraCT number	2018-001727-39
Trial protocol	HU
Global end of trial date	30 June 2021

Results information

Result version number	v1 (current)
This version publication date	11 January 2022
First version publication date	11 January 2022
Summary attachment (see zip file)	Summary of CSR, V2, dated 15 Jul 2021 (POP03_CSR_V02_summary_20210715.pdf) POP03_Synopsis_Protocol_Final_V01.1 (POP03_Synopsis_Protocol_Final_V01.1_clean_20180925.pdf)

Trial information

Trial identification

Sponsor protocol code	POP03

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Polpharma S.A. (Zaklady Farmaceutyczne Polpharma S.A.)
Sponsor organisation address	Peplinska 19, Starogard Gdanski, Poland, 83-200
Public contact	Eva Szucs, Appletree CIG-AG, +36 702450085, e.szucs@appletree-cig.com
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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	04 June 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 March 2020
Global end of trial reached?	Yes
Global end of trial date	30 June 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

PRIMARY OBJECTIVE
The primary objective of this study is to evaluate the efficacy and tolerability of Latanoprost Polpharma (test product) in lowering of IOP when compared to the originator Xalatan® (reference product).

Protection of trial subjects:

Safety and ocular tolerance of the test product was assessed by evaluating vital signs (blood pressure and heart rate), the ocular comfort level, conjunctival hyperemia, and other side effects (Adverse Events) of the test product in comparison to the reference product. The following study procedures and assessments were carried out according to established clinical practice: Dilated fundus examination, Slit lamp examination, Visual field testing, Visual acuity determination, Gonioscopy, Pachymetry. Patients were instructed to complete the daily medication diary card, indicating the time of dosing of each daily dose as well as any adverse experiences that may have occurred. Urine pregnancy tests are performed at the screening visit, at the Day 1 visits of both treatment periods, and at the final visit. Women of childbearing potential were only eligible for the study either if using an acceptable method of birth control for at least 28 days prior to the first dose and through the study or being heterosexually inactive (abstinent).

Background therapy:

Ongoing systemic therapies at study start were allowed to continue as long as the treatment regimen remained unchanged and the treatment was not expected to have an impact on IOP. Topical ocular treatment with lubricant eye drops (artificial tears) was allowed throughout the study.

Evidence for comparator:

The comparator in this trial is the medicinal product Xalatan ®, 50 micrograms/mL Eye drops, solution. 1 mL Eye drops solution contains 50 micrograms of latanoprost. One drop contains approximately 1.5 micrograms latanoprost. Excipients with known effect - Benzalkonium chloride 0.2 mg/mL is included as a preservative. The test product was a preservative-free generic version of Xalatan, and based on current regulations the present non-inferiority therapeutic equivalence study had to include the originator drug as reference (comparator).

Actual start date of recruitment	07 January 2019
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	Russian Federation: 16
Country: Number of subjects enrolled	Hungary: 33
Worldwide total number of subjects	49
EEA total number of subjects	33

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)	17
From 65 to 84 years	32
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Hungary: Site 01 - First Patient First Visit (FPFV): 7 Jan 2019, Last Patient Last Visit (LPLV): 4 Mar 2020; Site 02 - FPFV: 11 Feb 2019, LPLV: 25 Jun 2019; Site 03 - FPFV: 18 Jan 2019, LPLV: 4 Mar 2020; Russia: Site 04 - FPFV: 17 May 2019, LPLV: 11 Mar 2020; Site 05 - FPFV: 8 Apr 2019, LPLV: 20 Feb 2020

Pre-assignment

Screening details:

Main Inclusion Criterion - Ocular hypertension or primary open angle glaucoma in both eyes: mean diurnal IOP measured at -12, -8, –4, 0 hours pre-treatment on Day 1 must be higher than or equal to 22 mmHg, and lower than or equal to 34 mmHg (naïve or untreated, i.e., after washout of 28 days). 53 patients were screened in total in all five sites.

Pre-assignment period milestones

Number of subjects started	49
Number of subjects completed	49

Period 1

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

Blinding implementation details:

The non-masked primary packaging required investigator masking (Latanoprost Polpharma - in a HDPE bottle closed with a pump eye dropper, Xalatan® - in a dropper container of polyethylene with a screw cap). The site ensured that an independent professional not otherwise involved in the conduct of the study or not involved in the assessments or observations of the patients dispensed and collected the IPs ("unmasked site staff"). The subjects received drops with equal trial labels blinding IPs.

Arms

Arm title	all subjects

Arm description:

All subjects enrolled before randomization

Arm type	washout phase
Investigational medicinal product name	no IMP
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ocular use

Dosage and administration details:

no topical ocular drugs a were allowed other than artificial tears

Number of subjects in period 1	all subjects
Started	49
Completed	49

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

Blinding implementation details:
Investigators and assessorr masking was ensured

Arms	
Are arms mutually exclusive?	No
Arm title	Test

Arm description:
Latanoprost Polpharma: latanoprost 0.05 mg/ml, preservative free

Arm type	Experimental
Investigational medicinal product name	Latanoprost Polpharma
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops
Routes of administration	Ocular use

Dosage and administration details:
1 drop / day in the evening

Arm title	Reference

Arm description:
Xalatan (R) Pfizer

Arm type	Active comparator
Investigational medicinal product name	Xalatan (R)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ocular use

Dosage and administration details:
1 drop / day in the evening

Number of subjects in period 2	Test	Reference
Started	49	49
Completed	47	47
Not completed	2	2
Physician decision	1	1
Protocol deviation	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Washout
Reporting group description: all subjects enrolled	

Reporting group values	Washout	Total	
Number of subjects	49	49	
Age categorical			
Men and women 18-75 years old who can sign and date an Informed Consent.			
Units: Subjects			
from 18-84 years	49	49	
Age continuous			
All subjects, 18-75 years of age			
Units: years			
arithmetic mean	64.2		
standard deviation	± 9.8	-	
Gender categorical			
all subjects enrolled			
Units: Subjects			
Female	35	35	
Male	14	14	

Subject analysis sets	
Subject analysis set title	all subjects enrolled
Subject analysis set type	Per protocol
Subject analysis set description: all subjects enrolled	
Subject analysis set title	PP
Subject analysis set type	Per protocol
Subject analysis set description: all patients without major protocol deviation	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description: all patients which completed at least 1 treatment period	

Reporting group values	all subjects enrolled	PP	ITT
Number of subjects	49	44	47
Age categorical			
Men and women 18-75 years old who can sign and date an Informed Consent.			
Units: Subjects			
from 18-84 years	49	44	47
Age continuous			
All subjects, 18-75 years of age			
Units: years			

arithmetic mean	64.2		
standard deviation	± 9.8	±	±

Gender categorical			
all subjects enrolled			
Units: Subjects			
Female	35	32	34
Male	14	12	13

End points

End points reporting groups

Reporting group title	all subjects
Reporting group description:	
All subjects enrolled before randomization	
Reporting group title	Test
Reporting group description:	
Latanoprost Polpharma: latanoprost 0.05 mg/ml, preservative free	
Reporting group title	Reference
Reporting group description:	
Xalatan (R) Pfizer	
Subject analysis set title	all subjects enrolled
Subject analysis set type	Per protocol
Subject analysis set description:	
all subjects enrolled	
Subject analysis set title	PP
Subject analysis set type	Per protocol
Subject analysis set description:	
all patients without major protocol deviation	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
all patients which completed at least 1 treatment period	

Primary: reduction in mean diurnal IOP

End point title	reduction in mean diurnal IOP

End point description:

The secondary endpoint was the reduction of the mean diurnal IOP between Day 1 (baseline) and Day 29. The mean diurnal IOP was calculated as the average of the measurements performed at 12, 8, 4 and 0 hours before treatment on Day 1 and at 12, 16, 20 and 24 hours after treatment the previous day on Day 29.
In the ITT analysis (n=47), the reduction was 7.29 + 2.53 mmHg or 7.43 + 2.78 mm Hg after treatment with test or reference product, respectively. The fact that in both periods a marked IOP lowering effect was observed, which was even slightly superior to the one reported in literature demonstrates that the patient population under investigation was well responsive to the treatment.

End point type	Primary

End point timeframe:

Day 0 versus day 29

End point values	Test	Reference	PP	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	44	44	44	
Units: mm Hg				
arithmetic mean (standard deviation)	7.04 (± 2.14)	7.17 (± 2.11)	7.17 (± 2.11)	

Statistical analyses

Statistical analysis title	non-inferiority analyses
Comparison groups	Test v Reference
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	≤ 0.025
Method	Linear Mixed Model
Parameter estimate	Mean difference (net)
Point estimate	0.024
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.457
upper limit	0.504
Variability estimate	Standard error of the mean
Dispersion value	0.238

Secondary: reduction in man diurnal IOP

End point title	reduction in man diurnal IOP
End point description:	
End point type	Secondary
End point timeframe:	
Day 0 versus day 29	

End point values	Test	Reference	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	47	47	47	
Units: mm Hg				
arithmetic mean (standard deviation)	7.29 (± 2.53)	7.43 (± 2.78)	7.43 (± 2.78)	

Statistical analyses

Statistical analysis title	non-inferiority analysis
Statistical analysis description:	
non- inferiority analysis	
Comparison groups	Test v Reference

Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	≤ 0.025
Method	Linear Mixed Model
Parameter estimate	Mean difference (net)
Point estimate	-0.021
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.467
upper limit	0.434
Variability estimate	Standard error of the mean
Dispersion value	0.226

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The AEs were reported and recorded by PIs within 5 days at the latest.

Adverse event reporting additional description:

AEs were collected in clinical trial database and periodically reviewed by the study monitors on behalf of the sponsor. They were reported without exception in the clinical trial report.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23

Reporting groups

Reporting group title	All enrolled patients

Reporting group description:

Adverse events (AEs) and serious adverse events (SAEs) were reported from Visit 0 to Visit 8 using the AE form. The assessment of AEs included the type of AE (systemic/ocular), intensity, frequency, action taken, association with study medication, seriousness (SAE) and outcome. AEs were coded according to MedDRA (EN V 23.0). 118 AEs were reported - 65 ocular, 53 systemic (Table 15). AEs which occurred during the interim wash-out were associated with period I, as a causal relation to the test product administered in period I cannot be excluded. This explains partially the higher number of adverse events associated with period I. During the treatment with test product, 67 AEs were reported (37 ocular and 30 systemic), and during the treatment with reference product 51 adverse events were reported (28 ocular, 23 systemic; Table 15). In period I, 82 AEs were reported (43 ocular, 39 systemic), and in treatment period II, 36 AEs were reported (22 ocular, 14 systemic; Table 16).

Serious adverse events	All enrolled patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 49 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	All enrolled patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 49 (65.31%)		
Vascular disorders			
Migraine			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences (all)	6		
Nervous system disorders			

Headache subjects affected / exposed occurrences (all)	4 / 49 (8.16%) 28		
Eye disorders eye pain subjects affected / exposed occurrences (all)	25 / 49 (51.02%) 65		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	2 / 49 (4.08%) 3		

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? Yes

Date	Interruption	Restart date
01 March 2020	Because of the COVID-19 pandemic situation starting mid of March 2020, the study procedures had to be adapted. Due to specific request by the authorities in Hungary, the last monitoring visits and the close-out visits in this country had to be performed remotely, for which specific guidance documents were issued. Further site 04 in Moscow could, due to this situation, not be included in the first evaluation (CSR V1.0) as it was at the time under full quarantine and not accessible to the investigator, his staff or monitors. As a consequence, the respective study data could not be fully monitored and were thus not fit for inclusion in the former analysis. Importantly, the required number of 42 evaluable patients had also been reached without consideration of the 6 patients studied at this site. Therefore, the change had no impact on the validity of the Clinical Study Report V1.0. As mentioned in the Clinical Study Report V 1.0, the present report is the follow-up version of report V 1.0 , including the fully monitored and analysed data from site 04. In modification of the protocol, not only the non-inferiority of the test product when compared to the reference product with respect to the differences in mean diurnal IOP was determined, also the non-inferiority of the test product when compared to the reference product with respect to the difference for each measurement time point at baseline (-12, -8, -4 and 0 hours before treatment) and Day 29 (12, 16, 20 and 24 hours after treatment the previous day) was determined. This modification was reflected in the statistical analysis plan. The change was introduced as after finalizing of the clinical study protocol, it became apparent that increasingly authorities in Europe and overseas requested this data set for non-inferiority assessment of IOP lowering agents. The change has no impact on the validity of the study and its outcomes. On the contrary it even augments its validity.	01 May 2021

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to COVID-19, site 04 in Moscow was not included in the first evaluation (CSR V1.0) as it was at the time under full quarantine. The data of site 04 is included in the final CSR V2.0.

Notes: