ZAKLADY FARMACEUTYCZNE POLPHARMA SA

CLINICAL STUDY REPORT

Study title:

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

Product:	Generic latanoprost 0.05 mg/mL eye drops solution (Polpharma S.A.), preservative-free
Indication studied	Open angle glaucoma / ocular hypertension
Development Phase of Study:	Phase III - therapeutic equivalence trial
Short description of study:	Polpharma S.A. intends to develop a generic version of the ophthalmic medicinal product Xalatan® for Marketing Authorisation. The new product by Polpharma S.A. is a preservative-free formulation. The therapeutic equivalence trial evaluated the efficacy, safety and tolerability of latanoprost 0.05 mg/mL eye drops, solution (Polpharma S.A.) compared to the originator Xalatan® (latanoprost ophthalmic solution 0.005%, Pfizer) in order to show therapeutic non-inferiority and comparable safety and ocular tolerance of the generic product with respect to the originator product. The total study treatment duration for one patient was 58 days plus one inter-treatment wash-out period of 4 weeks plus one pre-treatment wash-out period of 0 or 4 weeks depending on the pre-treatment of the included patient. A total of 53 patients were recruited in 5 sites in 2 countries (Hungary and Russia).
IND Number/EudraCT Number	2018-001727-39
Clinical Trial Identification:	848300144/0103/1 - POP03
Study Initiation Date:	First Patient enrolled: 07 January 2019

Date of Early Study Termination (if any):	Not applicable
Study Completion:	Last Patient Completed: 13 March 2020
Study Report Version	Version 02
Release Date	15 July 2021
Replaces Previous Version:	Version 01

This clinical study was performed in compliance with current Good Clinical Practice (GCP) standards, all applicable laws and regulations; all essential documents are archived in the Clinical Trial Master File.

SPONSOR INFORMATION AND COORDINATING INVESTIGATOR

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CONFIDENTIALITY STATEMENT

2 SYNOPSIS

Name of Sponsor/company:	Zakłady Farmaceutyczne Polpharma SA
Name of Finished Product:	Generic Latanoprost Ophthalmic Solution 0.05mg/ml (Polpharma S.A.)
Name of Active Ingredient(s)	Latanoprost 0.05mg/ml
Title of Clinical Study:	A Phase III, Multicenter, Randomized, Investigator-Masked, Cross-Over, Comparative, Non-Inferiority Trial Evaluating the Efficacy and Tolerability of Generic Latanoprost Ophthalmic Solution 0.05mg/ml (Polpharma S.A.) Compared to Xalatan® (Latanoprost 0.005 % Ophthalmic Solution, Pfizer) in Patients with Ocular Hypertension or Primary Open Angle Glaucoma
Investigator(s) and Study Centres	A total of 53 patients were recruited in 5 sites in 2 countries (Hungary and Russia). Study sites: • **Site 01:** Jahn Ferenc Del-pesti Korhaz es Rendelointezet, Dept. of Ophtalmology Köves u. 1, 1204 Budapest, Hungary **PI:** Dr. Norbert Czumbel, Coordinating Investigator • **Site 02:** Ophthalmology Department, Hospital of Bacs-Kiskun County, H-6000 Kecskemet, Nyiri út 38., Hungary **PI:** Dr. Tamas Acs • **Site 03:** Markusovszky Egyetemi Oktatokorhaz, Dept. of Ophthalmology, Markusovszky u. 5, 9700 Szombathely, Hungary **PI:** Dr. Gyorgy Bator • **Site 04:** Pirogov Russian National Research Medical University, Ophthalmology Department, 1 Ostrovityanov st., Moscow, 117997, Russia **PI:** Prof. Dr. Evgeniy A. Egorov, • **Site 05:** Kirov Military Medical Academy of Ministry of Defense of the Russian Federation; 6 Acad. Lebedev str., Saint-Petersburg, 194044, Russia **PI:** Dr. Dmitrii Maltcev
Publications and References	List of References is in pt. 15 of CSR.
Studied Period:	Date of first enrolment: 07 January 2019 Date of last patient completed: 13 March 2020

Phase of Development	Phase III - therapeutic equivalence trial
Objectives	Primary Objective • The primary objective was to evaluate the efficacy of the generic latanoprost 0.05 mg/mL eye drops solution (Polpharma S.A.; test product) in lowering IOP when compared to the originator Xalatan® (latanoprost 0.005% ophthalmic solution, Pfizer; reference product). Secondary Objective(s) • To compare the ocular tolerance of the test and reference products using an ocular comfort level score. • To compare the levels of conjunctival hyperaemia induced by test product and reference product. • To evaluate safety in general as determined by vital signs and the incidence and nature of AEs of the test product compared to the reference product. • To evaluate the usability of the newly developed delivery device (newly developed dropper bottle) in a subgroup of the patients.
Methodology	The trial was set-up as a phase III, multicenter, randomized, investigator-masked, cross-over, comparative, non-inferiority trial. The included patients were naïve or previously treated with IOP lowering medication. The ones pre-treated with IOP lowering medication patients went through a 4-week wash-out period. The patients were assigned to receive either test or reference product in a 1:1 ratio during the treatment period I (29 days), followed by a wash-out period (28 days), before starting treatment period II (29 days). Patients who were assigned to receive test product in period I received reference product in period II and vice versa.
Number of Patients	Planned: 50 enrolled, 42 completed Analysed: 53 enrolled, 49 randomised; 47 completed
Indication	Glaucoma is an eye disorder in which the optic nerve suffers damage. It is often, but not always, associated with increased pressure of the fluid in the eye, the so-called aqueous humor. The term 'ocular hypertension' is used for cases having constantly raised IOP without any associated optic nerve damage or visual field defects. Elevated IOP above 21 mmHg is a significant risk factor for developing glaucoma. Untreated glaucoma leads to permanent damage of the optic nerve and resultant visual field loss, which can progress to blindness (Crick and Khaw, 2003).
Inclusion Criteria	• Age: 18-75 years old • Provision of signed and dated Informed Consent • General health conditions not interfering with participation in the study determined e.g., blood pressure, pulse rate and

	temperate at screening as assessed by the investigator • Female patients of childbearing potential should either be using acceptable methods of birth control or be heterosexually inactive (abstinent) for at least 28 days prior to the first dose and throughout the study • 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). The eye with the higher IOP will be selected as the study eye. If both eyes have the same IOP, the right eye will be selected. • Not on any ophthalmic pressure-lowering medication, or able to be withdrawn from current pressure-lowering medications for the washout periods as defined in this clinical trial protocol. • No clinically significant or progressive retinal disease. • No concomitant use of any topical ophthalmic medication other than artificial tears • No ocular glucocorticoids in the previous 3 months • No ocular trauma, surgery, inflammation or infection, no corneal foreign body in the previous 3 months • No systemic medication that may alter IOP in the previous 30 days (e.g., beta blockers, calcium channel blockers, ACE inhibitors, prostaglandins, etc.) or expected to continue the current treatment with these medicinal products on a stable regimen for the duration of the study. Patients who are contact lens wearers must agree not to use contact lenses for the duration of the study. The contact lenses must be removed prior to the first drug application.
Exclusion Criteria	• Corrected visual acuity of less than 20/100 in both eyes • Evidence of acute ocular infection, corneal foreign body, or ocular inflammation within 3 months of the screening visit. • History or evidence of severe inflammatory eye disease (i.e. uveitis, retinitis, scleritis, iritis) in one or both eyes; especially conjunctival hyperemia score at inclusion > 0 • Previous significant ocular trauma, laser or incisional surgery within 3 months of the screening visit • Traumatic cataract surgery with an open posterior capsule or any patient with an anterior chamber intraocular lens implant or aphakia IOP in either eye exceeding 34 mmHg (mean diurnal at Day 1: -12, -8, –4, -0 hours) • IOP in either eye greater than 34 mmHg at Day 1 (mean diurnal IOP measured at -12, -8, –4, 0 hours pre-treatment) • Any corneal abnormalities preventing reliable applanation

	tonometry • Central corneal thickness < 450 µm or > 600 µm. • Patients at risk of angle closure or evidence of acute, intermittent, or chronic angle closure • Forms of glaucoma resulting from conditions other than primary open-angle glaucoma or ocular hypertension, such as pigmentary or pseudo-exfoliative glaucoma • Pupil with inadequate ability to dilate sufficiently for peripheral retinal examination • History or evidence of Herpes simplex keratitis. • Patients with known risk factors for macular oedema. • Pregnant or nursing women or women who intend to become pregnant during the trial. • Patients who have participated in another research study for an investigational product or investigational medical device within 30 days of the screening visit. • History of drug or alcohol abuse within the last 6 months. • A history of hypersensitivity to latanoprost, or any component in the formulation of the products being tested. • History of evidence of any medical condition that would, in the opinion of the investigator, make the patient unsuitable for the study (i.e. severe hepatic, cardiovascular or renal impairment). Systemic medication that may alter IOP in the previous 30 days (i.e. beta-blockers, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, prostaglandins etc.) if the treatment regimen with these medicinal products is change during the study.
Test Product, Dose and Mode of Administration, Batch Number	Latanoprost Polpharma (latanoprost 0.05 mg/mL eye drops solution, Polpharma S.A.). Batch number: RF0344 The patients are treated with one drop of the test product into the affected eye(s) once a day in the evening every 24 hours between 20:00 and 22:00.
Reference Product, Dose and Mode of Administration, Batch Number	Xalatan® (latanoprost ophthalmic solution 0.005%, Pfizer) Batch number: W21226 T94250 (1st batch); X85074 X78911 (2nd batch) The patients are treated with one drop of the reference product into the affected eye(s) once a day in the evening every 24 hours between 20:00 and 22:00.
Duration of Treatment	The total study treatment duration for one patient was 58 days plus one inter-treatment wash-out period of 4 weeks plus one pre-treatment wash-out period of 0 or 4 weeks depending on the pre-treatment of the included patient.

Criteria for Evaluation	Primary Endpoint: Non-inferiority of test product when compared to the reference product with respect to the differences in the mean diurnal IOP in the study eye at baseline (measured at -12, -8, -4 and 0 hours before treatment) on Day 1 and Day 29 (12, 16, 20 and 24 hours after treatment the previous day). Non-inferiority margin is 1.5 mm Hg. IOP will be assessed using the Goldmann applanation tonometry. Secondary Endpoint(s) Efficacy: • Non-inferiority of test product when compared to the reference product with respect to the differences at each measurement time point at baseline (-12, -8, -4 and 0 hours before treatment) on Day 1 and Day 29 (12, 16, 20 and 24 hours after treatment the previous day). Non-inferiority margin is 1.5 mm Hg. Ocular Tolerance: • Difference between the investigational products with respect to ocular comfort level score at baseline (Day 1) and Day 29 • Difference between the investigational products with respect to conjunctival hyperaemia at baseline (Day 1) and Day 29. Safety: • Difference between the investigational products with respect to general safety as assessed by vital signs and the incidence and nature of adverse events. Usability: • Evaluation of usability of each of the delivery devices by the patients.
Statistical Methods	A statistical analysis plan was prepared prior to any data analysis. Non-inferiority of the test product in comparison with the reference product was tested using a mixed linear model. The effect of treatment (primary efficacy parameter) was calculated as the difference between the mean diurnal IOP in the study eye after 29+1 days of treatment and baseline (pre-treatment). As secondary efficacy parameters, the effect of treatment for each of the four measurement time points of the diurnal curve was calculated. The non-inferiority margin was set to 1.5 mmHg for the difference in treatment effect between the test and reference product. The efficacy analysis was performed on the PP population and repeated as sensitivity analysis on the ITT population to assess the robustness of the study results. The approach to testing non-inferiority was to use the two-sided 95% confidence interval for the difference (D) of the effects of the test and reference product: D = Effect (test) -Effect (reference) > - 1.5 mm Hg.

	Safety and ocular tolerance data were analyzed descriptively.
Summary and Conclusion	The test product, Latanoprost Polpharma, was shown to be non-inferior to the reference product, Xalatan ® using a linear mixed model non-inferiority analysis on the PP population (n=44). The difference in IOP lowering effect between the two treatments was highly non-significant (p-value 0.922 > 0.05) and the lower limit of the two-sided 95% confidence interval was within the non-inferiority margin (-0.457 > -1.5 mm Hg). The data even support non-inferiority against a margin of 1.0 mm Hg. The sensitivity analysis using the same linear mixed model on the ITT sample confirmed the non-inferiority of the test product compared to the reference product. The difference in IOP lowering effect between the two treatments at each individual measurement time point was also not significant for both, the PP and the ITT population. This very importantly confirms the robustness of the non-inferiority observed for the mean diurnal IOP and it confirms that the test product indeed is non-inferior to the reference product. The reduction in mean diurnal IOP between Day1 and Day 29 of between 7.3 and 7.4 mm Hg for both products in the ITT population (n=47) is well comparable and even slightly superior to published values for Xalatan® (6.7 + 3.4 mmHg; Camras, C., 1996), confirming that the patient population studied was responsive to the treatments. Both investigational products were equally well tolerated and safe as shown by the ocular tolerance level and hyperemia scores, as well as by the nature and incidence of adverse events and the absence of serious adverse events. The data show a trend in favor of the test product with regards to the severity of hyperemia and to the velocity of remission of ocular discomfort. Differences in the incidence of adverse event AEs were statistically not significant. The adverse events were mostly mild in nature and recovered well. Stinging or itching upon application, tearing eyes , blurred vision on installation, and ocular hyperemia are expected adverse events and were reported frequently for both products. The high incidences are likely related to the specific questioning after instillation. There is ever more evidence supporting the importance of unpreserved topical IOP lowering medications in order to avoid the side effects associated with preservatives. For young patients it is relevant because of their expected long-term treatment duration, for the elderly because of their already compromised ocular surface due to prior long-term topical therapy. This study clearly showed the non-inferiority of test product to the reference product in terms of IOP lowering and a trend in favor of for the test product regarding ocular tolerance signs and symptoms, as well as no statistically significant or clinically relevant differences regarding the occurrence and nature of

	adverse events. The usability assessment indicated clearly that there was no difference in user acceptance between the two products.
Date of report	15 July 2021

2.1.1 EFFICACY AND SAFETY MEASUREMENTS ASSESSED AND FLOW CHART

	Visit 0	4 weeks washout	**Visit 1**	**Tel.**	**Visit 2**	**Visit 3**	**Visit 4**	4 weeks washout	**Visit 5**	**Tel.**	**Visit 6**	**Visit 7**	**Visit 8**
	Screening		Baseline		Follow-up	Follow-up	End of Period I		Baseline		Follow-up	Follow-up	End of Period II End of Treat.
			Treatment period I						**Treatment period II**				
	Week -4		Day 1	Day 7 ±2 d	Day 14 ±1 d	Day 28 ±1 d	Day 29[2]		Day 1	Day 7 ±2 d	Day 14 ±1 d	Day 28 ±1 d	Day 29[2]
GENERAL													
Patient information and Informed Consent	x												
Demographic data	x												
Medical History	x												
Ocular History	x												
Inclusion and exclusion criteria	x		x										
On-site drug administration			x			x			x			x	
Home drug administration				← Once daily →						← Once daily →			
Vital signs: blood pressure, heart rate	x		x		x	x	x		x		x	x	x
Concomitant medication	x		x	x	x	x	x		x	x	x	x	x
Eligibility	x		x										
OCULAR ASSESSMENTS													
IOP (Goldmann)	x		-12, -8, -4 and 0 h				8 am, 12, 4, 8 pm		-12, -8, -4 and 0 h				8 am, 12, 4, 8 pm
Dilated fundus examination	x												
Slit lamp exam	x												
Visual field testing	x												
Visual acuity	x												

	Visit 0	4 weeks [1]	Visit 1	Tel.	Visit 2	Visit 3	Visit 4	4 weeks washout	Visit 5	Tel.	Visit 6	Visit 7	Visit 8
	Screening		Baseline		Follow-up	Follow-up	End of Period I		Baseline		Follow-up	Follow-up	End of Period II End of Treat.
			Treatment period I						Treatment period II				
	Week -4		Day 1	Day 7 ±2 d	Day 14 ±1 d	Day 28 ±1 d	Day 29[2]		Day 1	Day 7 ±2 d	Day 14 ±1 d	Day 28 ±1 d	Day 29[2]
Gonioscopy	x												
Pachymetry	x												
Ophthalmic concomitant medication	x		x	x	x	x	x		x	x	x	x	x
Ocular comfort (0, 5, 10, 20 minutes post dosing)			x			x			x			x	
Conjunctival hyperemia	x		x			x			x			x	
LABORATORY													
Pregnancy test (women of childbearing potential)	x		x						x				x
OTHER													
Telephone contact				x						x			
Adverse Events			x	x	x	x	x		x	x	x	x	x
Randomization to Investigational Product			x						x				
Distribute Investigational Product			x						x				
Weigh Investigational Product bottle			x				x		x				x
Distribute Patient Diary			x						x				
Patient compliance				x	x		x			x	x		x
Return Investigational Product / completed diary						x						x	
Usability questionnaire (subset)							x						x
End of study status													x

Table 1: Study flow chart

[1] not applicable to treatment-naïve patients[2] the day after day 28 ± 1 day

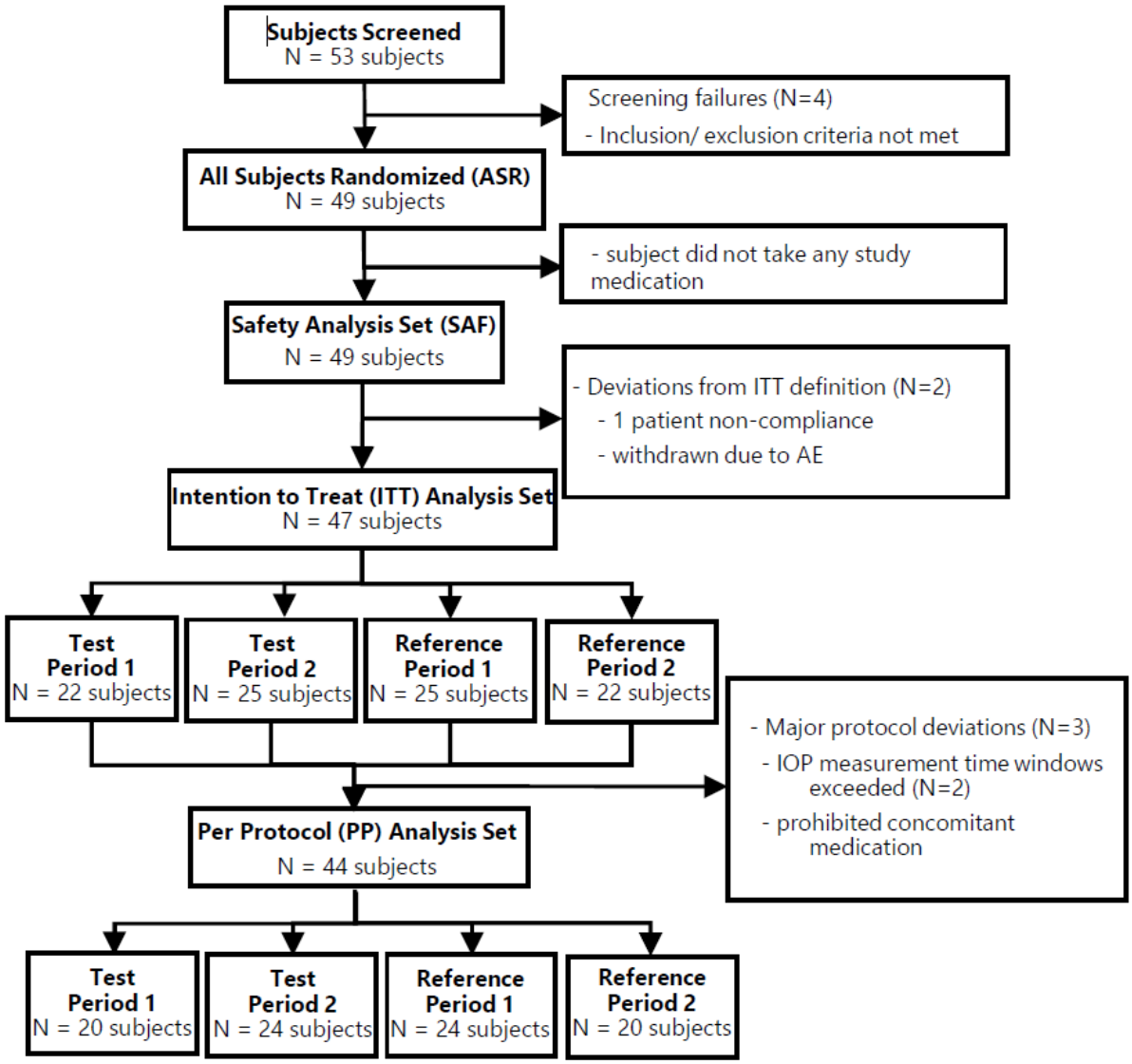

Figure 1: CONSORT flow diagram