PROTOCOL SYNOPSIS

Title:	A phase III, multicentre, randomized, investigator-masked, cross-over, comparative, non-inferiority trial 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.
Rational:	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 shall evaluate the efficacy 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.
Objective(s):	Primary Objective The primary objective is 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 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.
Endpoint(s)	Primary Endpoint(s) 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). IOP will be assessed using the Goldmann applanation tonometry. Secondary Endpoint(s) 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.
Study Design:	This is a phase III, multicentre, randomized, investigator-masked, cross-over, comparative clinical trial evaluating the efficacy and tolerability of the generic latanoprost 0.05 mg/mL eye drops solution (Polpharma S.A.) compared to the Xalatan® (latanoprost ophthalmic solution 0.005 %, Pfizer). After the screening visit, if the patient is eligible to participate in the trial, the patient will undergo a 4 - week washout, if the patient had a prior IOP lowering treatment. Patients who are treatment naïve will not need a washout. Patients will be randomly assigned in a 1:1 ratio to one of the treatment arms and treated for 29 days with the respective investigational product (first treatment period, period I). After an interim washout period of 4 weeks, the same patient will be treated for 29 days with the other investigational product (second treatment period, period II). Patients will be contacted on Day 7 of both treatment periods for a safety and compliance check. Also, patients will come to a safety visit on Day 14 (± 1 day) (safety assessment).

	The study is investigator-masked, i.e. an investigator who performs safety and efficacy assessments must not know which product the patient is / has been taking. Medication handling at site will be done by designated staff members only who are not involved in any of the safety and efficacy assessments. Patients will be requested to record the instillation of the ophthalmic solution daily in a patient diary. The diary will be checked for compliance.
Study Population:	A total of 50 patients will be recruited in approximately 5 sites in 2 countries (Hungary and Russia). 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 or (see point 5.2.1.1) • 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.
Study Assessments and Procedures:	**General** • Potential patients will be informed and asked to provide written informed consent before any study specific screening procedures are performed. • Study visits will be a screening visit (week -4 for patients on any IOP lowering medication, or any time before baseline assessment for treatment-naïve patients) and, during both treatment periods, baseline assessments (Day 1), follow-up visits (Day 14, Day 28 and Day 29), which results in a total of 9 visits. Patients will be contacted by phone on Day 7 of both treatment periods in order to assess potential adverse events.

	• To avoid bias, an investigator-masked design (single-blind) was chosen. The investigational products will be distributed and administered to the patients by trial staff not involved in any of the safety or efficacy assessments. **Summary of assessments to be performed:** **Efficacy** Efficacy of the reference product and the test product will be assessed by measuring the diurnal intraocular pressure (IOP) using Goldmann Applanation Tonometry. **Safety and Ocular Tolerance** Safety and ocular tolerance of the test product will be 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. **Usability** Usability will be evaluated by a sub-group of the patient population by assessment of usability of each of the delivery devices by the patients. **Additional Study Evaluations** The following study procedures and assessments will be carried out according to established clinical practice: • Medical history recording • Ocular history recording • Dilated fundus examination • Slit lamp examination • Visual field testing (only if not performed within 3 months prior to screening) • Visual acuity determination A complete listing of assessments and their timing can be found in the “Study Flow Chart”.

Investigational Product(s):	**Test Product:** Latanoprost Polpharma (latanoprost 0.05 mg/mL eye drops solution, Polpharma S.A.). 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:** Xalatan® (latanoprost ophthalmic solution 0.005%, Pfizer). 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. Patients will be requested to record the instillation of the ophthalmic solution daily in a patient diary. The diary will be checked for compliance.
Statistical analysis	Non-inferiority between the test product and the reference product will be tested using a mixed linear model using the Per Protocol Population. The effect of treatment will be calculated as the difference between the mean diurnal IOP in the study eye at Day 29 (average of the 4 measurements post-dosing) and at baseline (Day 1) (average of 4 measurements pre-dosing). The non-inferiority limit is set to 1.5 mmHg for the difference in treatment effect between the test and reference product. **Secondary Endpoints** To assess the safety endpoints ocular comfort and conjunctival hyperaemia at baseline (Day 1) and Day 29 the test product will be compared with the reference product using the nonparametric Mann-Whitney U test for independent samples or another statistical test, as appropriate. A 5% level of significance will be used to test for differences between the two treatments. All patients treated at least once with one investigational product will be evaluated (Safety Population).

	Incidence of adverse events will be analysed using Fisher's exact test for categorical data. **Sample Size** A sample size of 50 patients (including a 20% drop-out rate) was calculated to provide a 90% power that the 95% confidence interval of the difference in change of mean diurnal IOP from baseline (Day 1) to Day 29 between the two investigational products will be within 1.5 mmHg, assuming a treatment effect of 8.0 mmHg IOP reduction and a standard deviation of 3.0 mmHg and no real difference between the two products.