BMC Ophthalmology

RESEARCH Open Access

A phase III, multicentre, randomised, investigator-masked, cross-over, comparative, non-inferiority trial evaluating the efficacy and tolerability of generic preservative-free Latanoprost (Polpharma S.A.) compared to Xalatan® (Pfizer) in patients with ocular hypertension or primary open-angle glaucoma

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Abstract

Background Primary open-angle glaucoma (POAG), often associated with increased intraocular pressure (IOP), can lead to permanent damage of the optic nerve, concomitant visual field loss, and blindness. Latanoprost, a prostaglandin F2α analogue, reduces IOP and is used to treat glaucoma. In this clinical trial, we evaluated the efficacy of Latanoprost Polpharma, a generic preservative-free latanoprost 0.05 mg/ml eye drops solution, in lowering IOP when compared to the originator Xalatan® (latanoprost 0.005% ophthalmic solution, Pfizer).

Methods This was a Phase III, multicentre, randomized, investigator-masked, cross-over, comparative, non-inferiority trial carried out in 5 sites in Hungary and Russia. The primary endpoint was to evaluate the non-inferiority of the test product when compared to the reference product with respect to the differences in the mean diurnal IOP on Day 1 (baseline) and Day 29. The secondary endpoints included efficacy, ocular tolerance, safety, and usability. We recruited adult patients (18–75 years) with open-angle glaucoma or ocular hypertension.

Results Forty-nine patients were randomised and received at least one dose of the test or reference product. A virtually identical reduction of the mean diurnal IOP of 7.04 ± 2.14 mmHg or 7.17 ± 2.11 mmHg was found after treatment with test or reference product, respectively ($N = 44$). In the intention to treat analysis, the reduction was

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7.29 ± 2.53 mmHg (95% CI: 6.55–8.04) or 7.43 ± 2.78 mm Hg (95%CI: 6.61–8.24) after treatment with test or reference product, respectively (*N* = 47). There were no serious adverse events.

Conclusions Latanoprost Polpharma was shown to be non-inferior to Xalatan®. Both investigational products were equally well tolerated and safe. The data show a trend in favour of the test product with regards to the severity of hyperaemia and to the velocity of remission of ocular discomfort. Latanoprost Polpharma, being preservative-free, also avoids the cytotoxicity of benzalkonium chloride, the side effects of which may affect patient compliance and lower the quality of life.

Trial registration The study had the ethical and regulatory approval from the National Institute of Pharmacy and Nutrition (OGYEI, OGYEI/41,779- 11/2018) and the Ethics Committee for Clinical Pharmacology (KFEB) of Hungary and from the Ministry of Healthcare of the Russian Federation (MOH of Russia) prior to the beginning of the study (642/25.12.2018) (clinical trial identification number: 848,300,144/0103/1 - POP03; IND number/EudraCT number: 2018-001727-39).

Keywords Latanoprost, Glaucoma, Benzalkonium chloride

Background

Primary open-angle glaucoma (POAG) 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 humour. The term 'ocular hypertension' is used for cases having constantly raised intraocular pressure (IOP) without any associated optic nerve damage or visual field defects.

Untreated glaucoma leads to permanent damage of the optic nerve and concomitant visual field loss, which can progress to blindness. Elevated IOP above 21 mmHg is a significant risk factor for developing glaucoma and / or optic nerve damage and visual field loss [1]. The current treatments of POAG and ocular hypertension focus on reducing the IOP by lowering the production of aqueous humour or increasing outflow.

Latanoprost, a prostaglandin F2α analogue, reduces IOP by increasing aqueous outflow mainly via the uveoscleral pathway. Latanoprost was first developed and brought to market by Pfizer in 1996 under the trade name Xalatan®, an eye drops solution. Polpharma S.A. developed a generic version of latanoprost, called Latanoprost Polpharma, for marketing authorization.

Latanoprost Polpharma is a preservative-free (without benzalkonium chloride [BAK]) generic version of latanoprost indicated for the reduction of IOP in adult and paediatric patients with open-angle glaucoma or ocular hypertension. Several recent publications advise to use BAK-free ophthalmic solutions since there is substantial clinical benefit from removing BAK from ophthalmic preparations. A review of published literature confirms that after two weeks of treatment with latanoprost, steady state levels of its effect on IOP reduction are reached with very little fluctuation thereafter for up to 12 months [2, 3].

The primary objective of this clinical trial was to evaluate the efficacy of the generic, preservative-free latanoprost 0.05 mg/ml eye drop solution in lowering IOP when compared to the originator Xalatan® (latanoprost 0.005% ophthalmic solution).

Methods

Study design

This was a Phase III, multicentre, randomized, investigator-masked, cross-over, comparative, non-inferiority trial (clinical trial identification number: 848,300,144/0103/1 - POP03; IND number/EudraCT number: 2018-001727-39). The study was conducted between January 2019 and March 2020 in five sites in two countries: three sites in Hungary and two in Russia. The sites were evaluated, selected, and submitted for approval to the ethics committees and competent authorities. The study was designed to assess the non-inferiority of latanoprost Polpharma (test), a generic, preservative-free latanoprost 0.05 mg/ml solution, versus Xalatan® (reference), a latanoprost 0.005% ophthalmic solution, in accordance with the "Guideline on the Choice of the Non-Inferiority Margin", Sect. 3.2. "Two arm trials: test and reference" EMEA/CPMP/EWP/2158/99 (CHMP, 2005). Our study adheres to CONSORT guidelines.

Latanoprost s delivered in multi dose container: a high-density polyethylene bottle with 3 K dropper pump. The 3 K pump system is a patented dispensing apparatus with the main purpose to protect the contents from microbiological contamination. The fluid path is protected from microbiological contamination by a silver coil in the 3 K pump tip.

The study was investigator-masked, but since the primary packaging of the reference product was different from that of the test product, each site assigned unmasked personnel who were in charge of handling, distribution, and return of the investigational products. Both test and reference products were packaged and labelled identically with the exception of primary packaging. The patients were also instructed not to reveal the identity of the investigational products that they have

been assigned to the investigator or other personnel involved in the evaluation of the study outcomes.

This trial had a cross-over design. The sites received medication boxes, with printed randomization numbers. The designated site staff assigned the lowest available number to the patient and handed out the corresponding medication box to the patient. The patients who met the eligibility criteria on screening day were randomly assigned in a 1:1 ratio (using block sizes of 4) to be treated for 29±1 days with one of the two investigational products (period I). After a washout period of at least 28 days, the same patient was treated for 29±1 days with the other investigational product (period II) (Fig. 1). The wash-out phase of 4 weeks was chosen based on the FDA draft guidance on Brinzolamide [4].

A placebo group was not included, since there is ample evidence about the placebo effect in studies addressing the effect of topical medication on IOP using the Goldmann Applanation Tonometer. The effect is only a fraction of the effects observed in the study [5].

The primary endpoint was to evaluate the non-inferiority of the test product when compared to the reference product with respect to the differences in the mean diurnal IOP in the study eye on Day 1 (baseline) and Day 29. The non-inferiority margin was set to 1.5 mmHg for the difference in treatment effect between the test and reference product, which has been widely used in comparable studies with IOP lowering agents.

The primary efficacy parameter was the mean diurnal IOP. IOP was determined using a Goldmann Applanation Tonometer under local anaesthesia and following established procedures at the site. Two IOP measurements were done at each time point and the mean thereof was recorded as the IOP value at that corresponding time point. Since the IOP is known to vary naturally over the course of the day, 4 different IOP measurements were taken (approx. at 08.00, 12.00, 16.00, and 20.00 h) at baseline and at the end of the treatment in each treatment period to calculate the mean diurnal IOP. These four timepoints were chosen based on the data by Camras, who showed that a plateau of low IOP was reached after the third measurement at approximately 16.00 [2]. The IOP lowering effect was then calculated as the difference in the mean diurnal IOP in the study eye between Day 1 and Day 29.

The secondary endpoints included efficacy, ocular tolerance, safety, and usability. With respect to efficacy, we investigated the non-inferiority of the test product when compared to the reference product with respect to the differences in IOP at each measurement time point on Day 1 and on Day 29. We also investigated the difference between the investigational products with respect to ocular comfort level score and conjunctival hyperaemia on Day 1 and Day 29. The scale to rate the ocular comfort level was as follows: 0=no discomfort; 1=mild discomfort disappearing within 20 min after treatment; 2=moderate discomfort, i.e., no medical intervention needed, expected to disappear within one hour; 3=severe discomfort, medical intervention needed; 4=very severe discomfort, medical intervention needed, use of investigational product is interrupted or discontinued. Ocular comfort was assessed immediately post dose (0 min), 5, 10, and 20 min post dose on Day 1 and Day 28 in both treatment periods. Hyperaemia was evaluated by performing a slit lamp examination 20 min post dose. It was described using the following scores: 0=no conjunctival hyperaemia, vessels normal; 1=sporadic vessels clearly injected above normal; 2=diffuse red eye with individual vessels dilated but still discernible; 3=intensive red eye with strong dilation of conjunctival vessels, which are no longer easily discernible.

To assess safety, we investigated the difference between the investigational products with respect to general safety as assessed by vital signs and the incidence and nature of adverse events (AEs). Vital signs were determined by measuring blood pressure and heart rate after 3 min in sitting position following established procedures at the site. AEs were coded according to MedDRA (English Version 23.0). The patients evaluated the usability of each of the delivery devices by means of a questionnaire with eight scoring questions (scale 1–10) and three free text

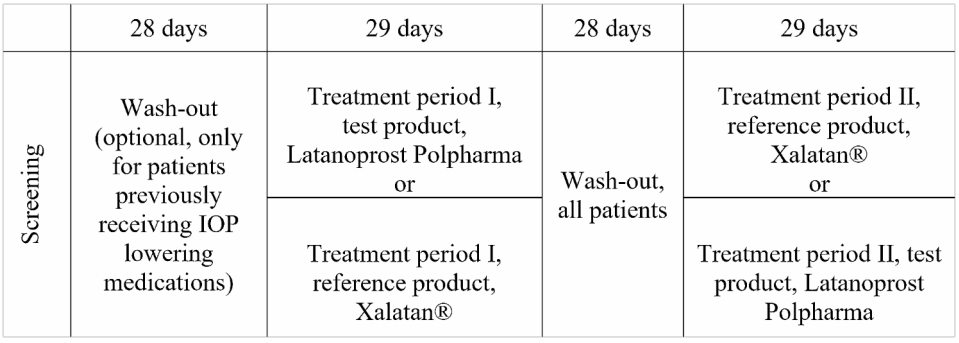

Fig. 1 Cross-over design and treatment periods. Test product Latanoprost Polpharma; reference product Xalatan®

questions, which the patients completed at the end of each period.

Ethical approval

The study had the ethical and regulatory approval from the National Institute of Pharmacy and Nutrition (OGYEI, OGYEI/41,779- 11/2018) and the Ethics Committee for Clinical Pharmacology (KFEB) of Hungary and from the Ministry of Healthcare of the Russian Federation (MOH of Russia) prior to the beginning of the study (642/25.12.2018). The study was conducted in accordance with the ICH guidelines for Good Clinical Practice (GCP, E6) and the Declaration of Helsinki (Version 6 of 64th General Assembly of WMA in Fortaleza, Brazil 2013). Data management was conducted in compliance with Good Clinical Data Management Practices.

Participant recruitment and consent

A total of 53 patients aged 18–75 years old with open-angle glaucoma or ocular hypertension were recruited. The inclusion criteria were as follows: age: 18–75 years old; provision of signed and dated Informed consent; general health conditions not interfering with participation in the study (e.g. blood pressure); female patients of childbearing age 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 POAG in both eyes: mean diurnal IOP measured at -12, -8, -4, 0 h 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); not on any ophthalmic pressure-lowering medication, or able to be withdrawn from current pressure-lowering medications for the washout periods; no clinically significant or progressive retinal disease as determined by dilated peripheral retinal examination done at screening; 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 were contact lens wearers had to agree not to use contact lenses for the duration of the study.

Patients were excluded from the study if they fulfilled any of the following criteria: a corrected visual acuity of less than distance Snellen 20/100 corresponding to decimal 0.20 or log MAR 0.70 in both eyes; evidence of acute ocular infection, corneal foreign body, or ocular inflammation within 3 months of the screening visit; a history or evidence of severe inflammatory eye disease in one or both eyes, especially conjunctival hyperaemia 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 h); IOP in either eye greater than 34 mmHg at Day 1 (mean diurnal IOP measured at -12, -8, −4, 0 h 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 if the treatment regimen with these medicinal products is changed during the study.

Informed consentwas obtained from all the patients included in the study prior to any study-related activities and in accordance with all applicable regulatory requirements. The investigator and/or his/her designee orally informed every patient in addition to the written patient information about all aspects of the patient's participation in the study. The competent ethics committees and regulatory authorities approved the written patient information and informed consent form, according to the local regulations of the European Union, Hungary, and Russia.

Timeline for both treatment periods

On Day 1, the patient reported to the clinic, where the IOP was measured at four different timepoints and the first dose of the assigned investigational product was administered. Thereafter, patients were instructed to instil one drop of the investigational product into the affected eye(s) once a day, with an interval as close as possible to 24 h between 20:00 and 22:00. The patients

also were given diary cards which they were asked to complete at home in order to document medication compliance.

Follow-up visits took place on Day 14, Day 28, and Day 29 of both periods. Patient compliance was documented in the patients' diaries and by weighing the bottles at the beginning of each treatment period and at the end of the treatment period by the unmasked site staff. In addition, patients were contacted by phone on Day 7(±2) to enquire about their well-being and to assess compliance. A maximum of 20% missed doses during one treatment period was considered acceptable for per protocol evaluation.

Patients experiencing any of the following did not receive further dosing of test or reference product: confirmed pregnancy or wish to become pregnant; mean diurnal IOP higher than 34 mmHg in either eye; anaphylaxis; severe adverse reaction; severe inflammatory eye disease in one or both eyes; non-compliance to study procedures.

Statistical analysis

A sample size of 50 patients (including a 20% drop-out rate) was calculated to provide 90% power that the 95% confidence interval of the difference in change of mean diurnal IOP from baseline to Day 29 between the two products will be within 1.5 mmHg, assuming a treatment effect of 8 mmHg IOP reduction and a standard deviation of 3 mmHg and no real difference between the two products. Assuming an attrition rate of approximately 20% (drop-outs, protocol deviations) a total of 42 evaluable patients was found to be needed. The sample size was calculated using the ExpDesign Studio 5.0.2 Software referenced in the book by Chang [6].

A total of 49 patients were included in the analysis (safety [SAF] population). Of these, 47 were evaluable for the efficacy endpoints (intention to treat [ITT] population). The efficacy analysis included data from all patients completing the study according to the protocol without major protocol deviations (per protocol [PP] population), as well as from all patients completing the study (ITT population). The safety analysis included data from all patients that received at least one dose of the investigational products (Fig. 2).

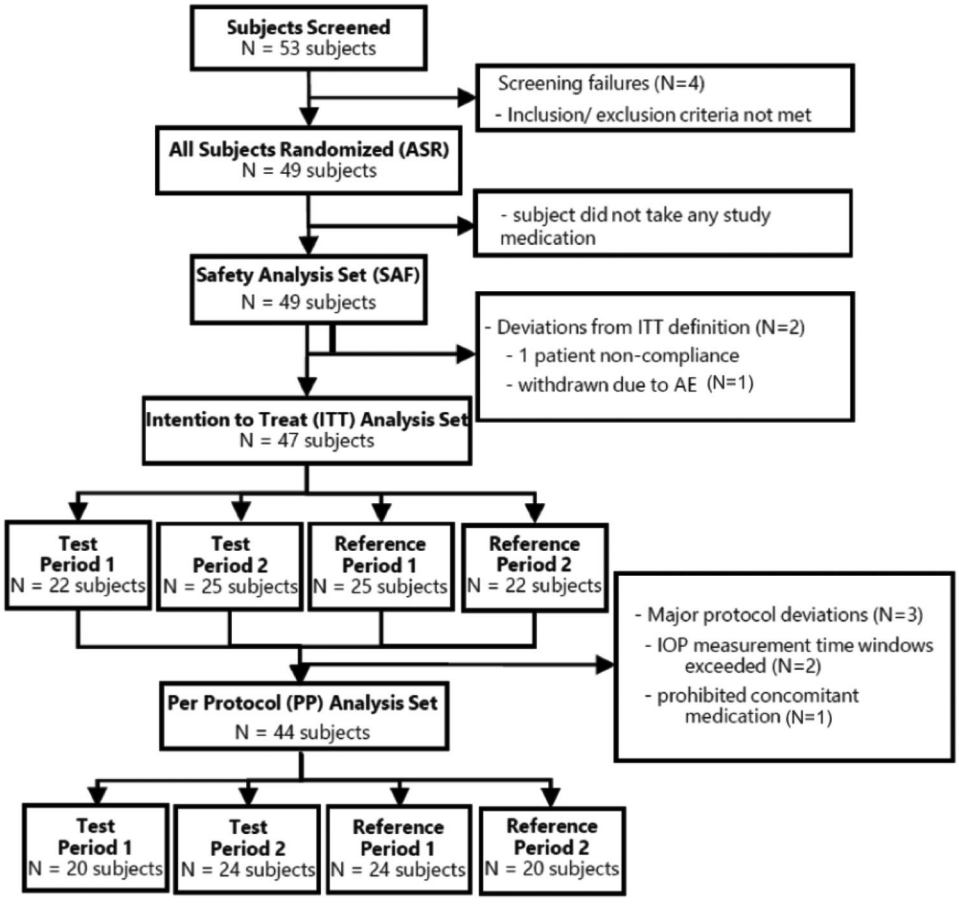

Fig. 2 CONSORT flow diagram

The non-inferiority of the test product in comparison with the reference product was tested using a mixed linear model. The goal was to reject the null hypothesis H0 at the one-sided significance level $\alpha = 0.025$. The approach to testing non-inferiority was to use the two-sided 95% confidence interval (CI) for the difference (D) of the effects of the test and reference product:

D = Effect (test) -Effect (reference) > -1.5 mm Hg.

This was done using the following non-inferiority hypotheses:

H0: Test – Reference ≤ – 1.5 mmHg (Test is inferior to Reference).
Ha: Test – Reference > – 1.5 mmHg (Test is not inferior to Reference).

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 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. Safety and ocular tolerance data were analysed descriptively.

Changes to methods after trial commencement

The study procedures had to be adapted because of the COVID-19 pandemic, starting mid March 2020. Due to a 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.

In modification of the protocol, the non-inferiority of the test product when compared to the reference product was investigated not only with respect to the differences in mean diurnal IOP but also with respect to the difference for each measurement time point at baseline (-12, -8, -4 and 0 h before treatment) and Day 29 (12, 16, 20 and 24 h after treatment the previous day) was determined. This modification was reflected in the statistical analysis plan. The change was introduced because it became apparent that authorities in Europe and overseas increasingly requested this data set for the non inferiority assessment of IOP lowering agents. The change has no impact on the validity of the study and its outcomes.

Table 1 Baseline characteristics of the patients per treatment sequence

Treatment sequence	*N*	Age years ± SD	Gender *n* (%)		Ethnicity *n* (%)
			Female	Male	Caucasian/White
Test - reference	23	65.9 ± 8.2	16 (69.6%)	7 (30.4%)	23 (100%)
Reference - test	26	62.7 ± 11.3	19 (73.1%)	7 (26.9%)	26 (100%)

Results

A total of 53 patients were screened in all five sites. Four of them were screening failures. Forty-nine patients were randomised and received at least one dose of the test or reference product (SAF). Two patients were withdrawn from the study before the end of treatment period I, which excluded them from the ITT population (ITT = 47 patients). One withdrawal was due to an AE (cystoid macular oedema) and the other due to non-compliance of the patient. Protocol deviations led to the exclusion of 3 patients from the PP population (PP = 44 patients).

The mean age ± standard deviation (SD) of the study population (SAF) was 64.2 ± 9.8 years. Most of the patients were women (71.4% female, 28.6% male). Due to the cross-over design, differences in age or gender between the groups were not relevant. All patients were Caucasian, which was to be expected because the study sites were in Europe (Hungary and Russia). There were no significant differences between the sequences with respect to all demographic parameters, including age, gender, height, and weight (Table 1).

Patient compliance was very high in both periods. None of the patients missed more than two doses. In period I > 95% of the patients reported having taken all the doses, and in period II > 90% of the patients were fully compliant.

Efficacy analyses

The primary endpoint was the reduction of the mean diurnal IOP between Day 1 and Day 29. In the PP analysis, a virtually identical reduction of the mean diurnal IOP of 7.04 ± 2.14 mmHg (95% CI: 6.39–7.69 mmHg) or 7.17 ± 2.11 mmHg (95% CI: 6.52–7.81 mmHg) was found after treatment with test or reference product, respectively ($N = 44$; Fig. 3). In the ITT analysis, the reduction was 7.29 ± 2.53 mmHg (95% CI: 6.55–8.04 mmHg) or 7.43 ± 2.78 mm Hg (95%CI: 6.61–8.24 mmHg) after treatment with test or reference product, respectively ($N = 47$).

Secondary efficacy endpoints were the reductions of IOP between Day 1 and Day 29 for each measurement time point (Fig. 4). In both, the PP and the ITT populations, the reductions between Day 1 and Day 29 at each time point were very similar.

Primary efficacy endpoint

The non-inferiority of the test product was demonstrated in the PP population using a mixed linear model ($n = 44$, 88 periods). The difference between the two treatments

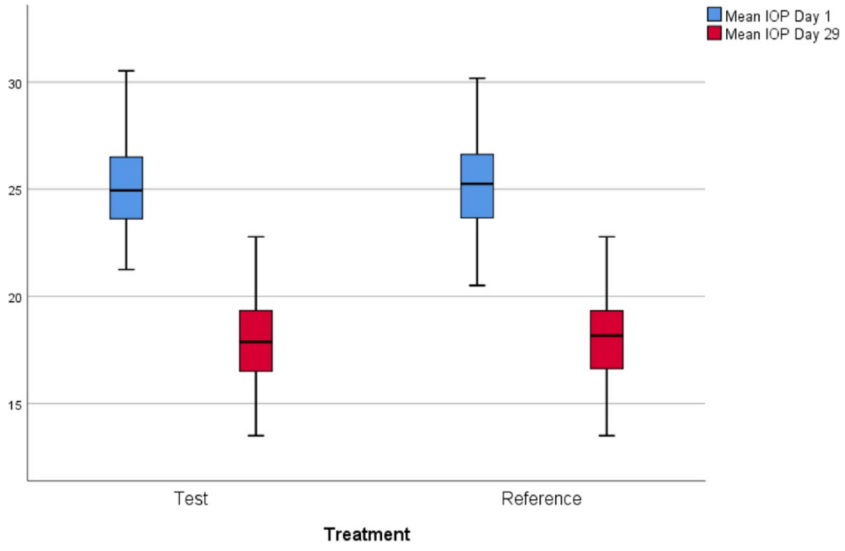

Fig. 3 Boxplot of mean diurnal IOP at Day 1 and Day 29 by treatment (PP)

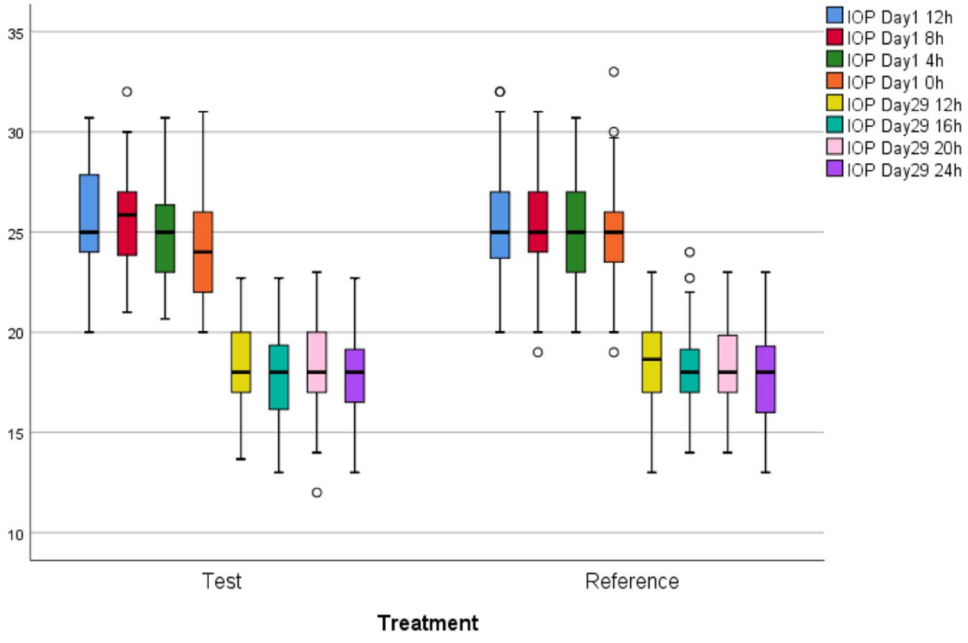

Fig. 4 Boxplot of IOP measurements at Day 1 (8 h, 6 h, 0 h pre-dose) and Day 29 (0 h, 2 h, 8 h post dose) by treatment and period (PP)

with respect to the mean diurnal IOP was highly non-significant (p-value 0.922; Fig. 5). The two-sided 95% CI for the treatment difference was (-0.457, 0.504 mmHg). The lower limit of the CI (-0.457 mm Hg) was greater than −1.5 mmHg (the noninferiority margin), indicating non-inferiority of test when compared to reference.

The two-sided 95% CIs for the treatment effects were (6.610, 7.699 mm Hg) for test and (6.587, 7.675 mm Hg) for reference.

For analysing the sensitivity of the data set, the same mixed linear model was applied to the ITT population (n=47, 92 periods). The null hypothesis that the test product is inferior to the reference product could again be rejected since the lower limit of the CI (-0.477 mm Hg) was greater than the non-inferiority margin (−1.5 mm Hg). The confirmation of the non-inferiority in the ITT population, which also includes patients with major protocol deviations, is a sign for the robustness of the data presented.

Secondary efficacy endpoints

In the PP population, the non-inferiority of the test product was demonstrated for all timepoints using a mixed linear model (n=44, 88 periods). The difference between

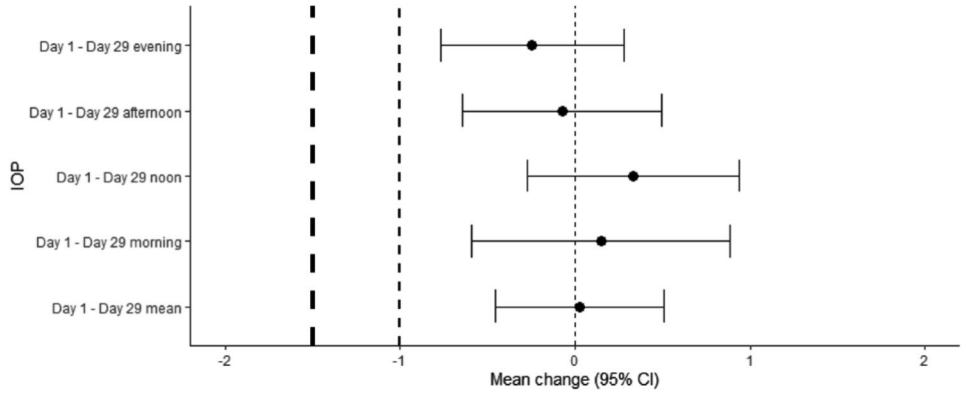

Fig. 5 Two-sided 95% Confidence intervals and non-inferiority margins (PP)

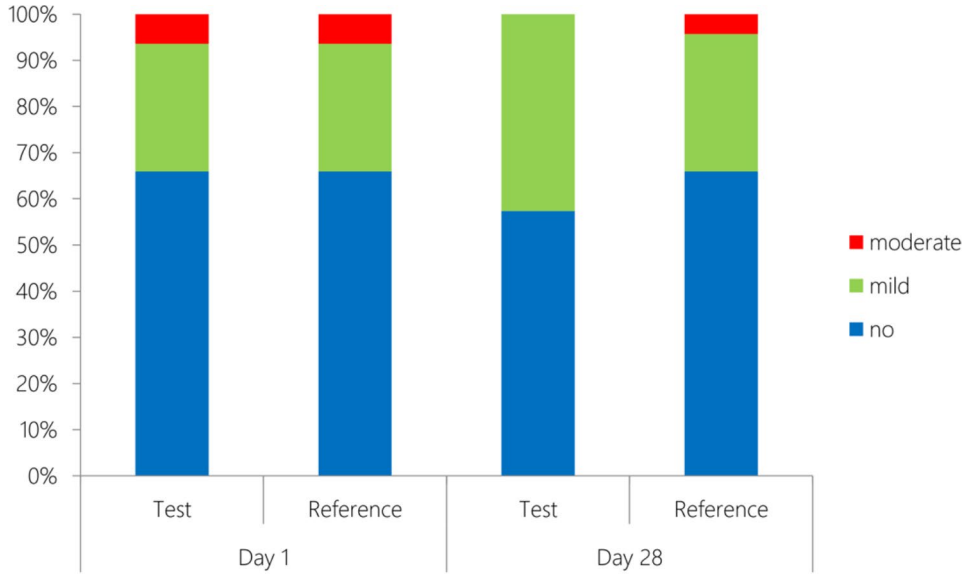

Fig. 6 Maximal ocular discomfort on Day 1 and Day 28 by treatment (ITT population)

the two treatments with respect to mean diurnal IOP was not significant (p-values between 0.271 and 0.790, all >0.05). The lower limits of the two-sided 95% CIs for the treatment differences were between −0.272 and −0.772 (Fig. 5), all greater than −1.5 mmHg (the non-inferiority margin), indicating non-inferiority of test when compared to reference for all time points. The data even demonstrate non-inferiority against a margin of 1.0 mmHg for all time points. Non-inferiority was also confirmed for all time points in the ITT population.

Secondary objectives

With regard to ocular comfort levels (Fig. 6; ITT population), two thirds of the patients reported no discomfort on Day 1 (test and reference each 66.0%), and over 55% of the patients reported no discomfort (test: 57.4%; reference 66.0%) on Day 28. The same proportion of patients in the test and reference groups reported mild or moderate discomfort on Day 1, whereas on Day 28 slightly more patients reported mild discomfort during test treatment (test: 42.6%; reference 29.8%). On Day 28, no patients treated with test product reported moderate discomfort, but 2 patients treated with reference product (4.3%) did. The discomfort reported immediately after instillation was transient, as seen with the increase of patients reporting no discomfort in consecutive assessments after 5, 10, and 20 min. On Day 1, twenty minutes after instillation, 97.9% of the patients treated with test product and 93.6% of the patients treated with reference product reported no ocular discomfort, and on Day 28, 100.0% of the patients treated with test product and 87.2% of the patients treated with reference product reported no discomfort after 20 min. The data show a trend in favour of the test product with regards to remission of initial ocular discomfort.

With respect to conjunctival hyperaemia (Fig. 7; ITT population), almost to 70% of the patients were found to have no hyperaemia on Day 1 (test: 68.1%; reference:

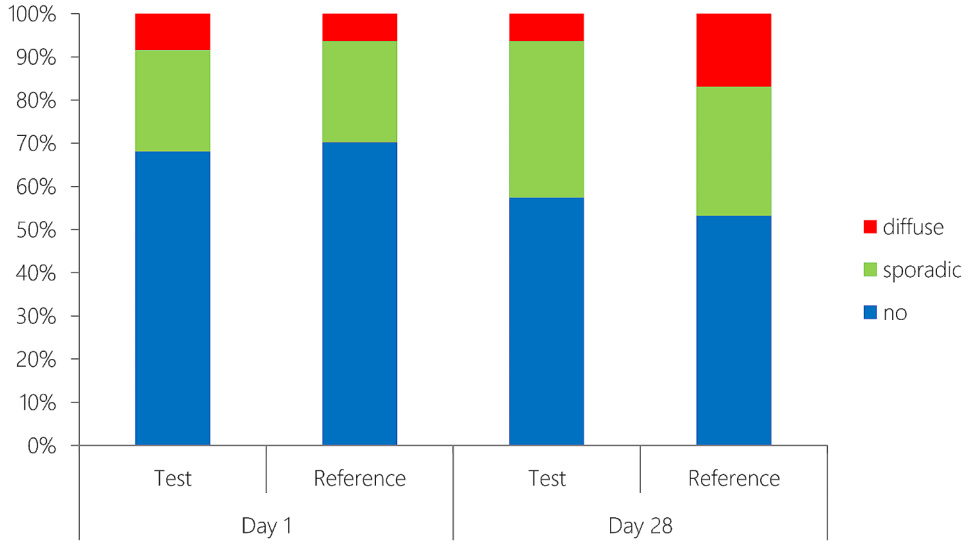

Fig. 7 Maximal conjunctival hyperaemia on Day 1 and Day 28 by treatment (ITT Population)

Table 2 Adverse events – ocular or systemic by treatment (multi-response)

Treatment		Test		Reference		Total	
		N	%	N	%	N	%
AE	Ocular	37	55.2%	28	54.9%	65	55.1%
	Systemic	30	44.8%	23	45.1%	53	44.9%
	Total	67	100.0%	51	100.0%	118	100.0%

70.2%), and over 50% of the patients had no hyperaemia (test: 57.4%; reference 53.2) on Day 28. Essentially the same proportion of patients were diagnosed with sporadic vessels or diffuse red eye on Day 1, whereas on Day 28 slightly more patients had sporadic vessels during test treatment (test: 36.2%; reference 29.8%). On day 28, three patients (6.4%) treated with test product and eight patients treated with reference product (17.0%) were found to have diffuse red eye. The data indicate a trend in favour of the test product as regards the severity of hyperaemia. No reports of "intensive red eye" were made.

Safety analysis

A total of 118 AEs were reported, of which 65 were ocular and 53 systemic (Table 2). Most AEs were mild or moderate, only one AE was severe (left knee pain considered not related to the study treatments). A total of 58 AEs (49.2%) were considered not related or unlikely related to the study treatments (test: 36; reference: 22), and 60 AEs were considered definitely related, probably related, or possibly related (test: 31; reference: 29). Most of the ocular AEs were considered definitely related, probably related, or possibly related, while most of the systemic AEs were considered not related or unlikely related. Only one patient had to discontinue treatment due to an AE (cystoid macular oedema).

Most of the ocular AEs were commonly known or expected in association with latanoprost, such as stinging or tearing upon application, blurred vision on instillation, itching of the eye(s), abnormal sensitivity of the eye to light, or dysgeusia. The three most frequently occurring AEs were "eyes stinging", "eye itching," and "tearing eyes" (test: 54%; reference: 57.2%), all expected. Overall, the tolerance as judged by the reported ocular AEs seems to be very similar between the two treatments.

Headache was the most frequently reported systemic AE (test: 46.7%; reference: 47.8%). All the other systemic AEs were rare (occurring twice) or singular incidences. No serious AEs occurred during the study.

The study was not powered to detect statistically significant differences in the occurrence of AEs. Nevertheless, there was no statistically significant difference regarding the occurrence of AEs between test and reference treatment.

Usability assessment

There was no difference between the two delivery devices. The test device was just as easy to use for the patients as the traditional device used with the reference product.

Discussion

Both investigational products were equally well tolerated and safe as shown by the ocular tolerance level and hyperaemia scores, as well as by the nature and incidence of AEs and the absence of serious AEs. 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 partially explains the higher number of AEs associated with period I.

An important difference between test and reference products is the lack of preservatives in the test product. There is ever more evidence supporting the importance of unpreserved topical IOP-lowering medications in order to avoid the side effects associated with preservatives. BAK, a quaternary ammonium compound, is the most frequently used preservative in eye drops, where it acts as an antimicrobial and antifungal agent. However, it is also known to be toxic to human cells, and many reports in the literature associate its use with inflammation [7] and cell damage [8]. Its prolonged use can cause or aggravate ocular surface disease. Moreover, BAK has been shown to penetrate beyond the ocular surface and into deeper tissues, specifically the trabecular meshwork and the optic nerve [9].

The concentration at which BAK starts having a cytotoxic effect has been estimated at ~0.005%, yet it is added to ophthalmic preparations in concentrations of 0.004–0.025% [10] (including Xalatan®, which has a BAK concentration on the higher end of the spectrum at 0.02%). Its toxic effects have been reported in corneal, conjunctival, trabecular meshwork, and ciliary epithelial cells, both in vitro [11] and in animal models [8, 12]. Clinical studies have shown that BAK-containing glaucoma preparations are associated with more ocular AEs than preservative-free alternatives. Furthermore, these symptoms decreased when patients using eyedrops with preservatives were switched to preservative-free drops or had the number of instillations reduced [12–16].

Baudouin et al. [10] summarized the ocular surface side effects and toxicity of BAK-containing topical treatments, including tear film instability, loss of goblet cells, conjunctival squamous metaplasia and apoptosis, disruption of the corneal epithelium barrier, and damage to deeper ocular tissues. The mechanisms through which BAK exerts its cytotoxicity are not clear, but inflammatory processes are thought to be involved [17], and it is also known to interact with the lipid components of the tear film and cell membranes. Others have suggested that BAK, having a positive charge, interacts with mitochondria, which are the only negatively charged intracellular structure [12]. For a recently published review on the problems of the use of BAK in eye medications, including the cytotoxic effects of BAK on ocular tissues, possible mechanisms of action, and clinical symptoms see Goldstein et al. [12].

The side effects associated with BAK are relevant for patients of all ages: for the young because of their expected long-term treatment duration and for the elderly because of their already compromised ocular surface due to prior long-term topical therapy. These side effects include pain or discomfort during instillation, foreign body sensation, stinging or burning, and dry eye sensation, all of which may affect patient compliance and lower the quality of life. Hence the importance of preservative-free alternatives, like Latanoprost Polpharma, which have been shown to improve ocular symptoms while maintaining the reduction in IOP achieved by preserved preparations [14].

This study clearly showed the non-inferiority of test product to the reference product in terms of IOP lowering and a trend in favour of the test product regarding ocular tolerance signs and symptoms, as well as no statistically significant or clinically relevant differences regarding the occurrence and nature AEs. The usability assessment indicated clearly that there was no difference in user acceptance between the two products. The reduction in mean diurnal IOP between Day 1 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) [2], confirming that the patient population studied was responsive to the treatments.

Conclusion

Latanoprost Polpharma was shown to be non-inferior to the reference product, Xalatan®, while avoiding the side effects associated with preservatives. The sensitivity analysis confirmed its non-inferiority compared to the reference product. The difference in IOP lowering effect between the two treatments at each individual time point was also not significant. Both investigational products were equally well tolerated and safe. The data show a trend in favour of the test product with regards to the severity of hyperaemia and the velocity of remission of ocular discomfort. The use of preservatives, and specifically BAK, is associated with side effects that can aggravate ocular disease and negatively affect patient compliance and quality of life. Hence, the preservative-free nature of the test product is a major advantage over the reference product.

Abbreviations

AEs	Adverse events
BAK	Benzalkonium chloride
CI	Confidence interval
IOP	Intraocular pressure
ITT	Intention to treat
POAG	Primary open-angle glaucoma
PP	Per protocol

SAF Safety analysis
SD Standard deviation

Acknowledgements
The Authors would like to thank Marisa Granados from Proper Medical Writing Sp. z o.o., Warsaw, Poland, for medical writing of this paper and Dorota Szymańska from Proper Medical Writing Sp. z o.o., Warsaw, Poland, for editorial assistance of this paper.

Author contributions
N.C., T.A., G.B., A.H., E.E., and D.M. contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript.

Funding
The medical writing of this article was funded by Polpharma Polska.

Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study had the ethical and regulatory approval from the National Institute of Pharmacy and Nutrition (OGYEI, OGYEI/41779- 11/2018) and the Ethics Committee for Clinical Pharmacology (KFEB) of Hungary and from the Ministry of Healthcare of the Russian Federation (MOH of Russia) prior to the beginning of the study (642/25.12.2018). The study was conducted in accordance with the ICH guidelines for Good Clinical Practice (GCP, E6) and the Declaration of Helsinki (Version 6 of 64th General Assembly of WMA in Fortaleza, Brazil 2013). Data management was conducted in compliance with Good Clinical Data Management Practices.

Consent for publication
Not applicable.

Informed consent
Informed consent was obtained from all the patients included in the study prior to any study-related activities and in accordance with all applicable regulatory requirements. The investigator and/or his/her designee orally informed every patient in addition to the written patient information about all aspects of the patient's participation in the study.

Competing interests
The authors declare that they have no competing interests.

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Received: 19 December 2023 / Accepted: 17 July 2024
Published online: 29 July 2024

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