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CLINICAL TRIAL REPORT

# Fifteen-Month Outcomes of Preservative-Free Latanoprost Cationic Emulsion in Open-Angle Glaucoma and Ocular Hypertension: Phase III Open-Label Extension of a Randomized Trial

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**Purpose:** Reporting of open-label extension data following a Phase III, randomized study examining treatment outcomes with preservative-free latanoprost eye drop cationic emulsion and preserved latanoprost in patients with open-angle glaucoma (OAG)/ocular hypertension (OHT).

**Patients and Methods:** OAG/OHT patients were randomized 1:1 to receive preservative-free latanoprost 0.005% eye drop emulsion or preserved latanoprost 0.005% for 12 weeks. Patients entering the extension study received open-label preservative-free latanoprost eye drop emulsion from Week 12 through Month 15. Endpoints included mean (standard deviation [SD]) change from baseline (Day 1, post-washout) in peak (9:00 AM ± 1 hour) intraocular pressure (IOP), corneal fluorescein staining (CFS; modified Oxford Grade Scale) score, ocular surface disease (OSD) symptom score and adverse event (AE) reporting.

**Results:** Respective mean (SD) peak (9:00 AM) IOP reductions from baseline at Week 12, and Months 6, 9 and 15 were 8.9 (3.0), 8.9 (3.0), 9.0 (2.7) and 8.7 (2.3) mmHg for preservative-free latanoprost eye drop emulsion users (N=70) and 7.8 (2.6), 8.3 (2.6), 8.1 (2.7) and 7.6 (2.8) mmHg for patients switching from preserved latanoprost at Week 12 (N=66). Between-group differences for the change in IOP were statistically significant at Week 12 (–1.06; nominal $p$=0.029). Mean CFS and OSD symptoms scores were reduced in both groups through Month 15. No serious treatment-related AEs were reported during the study period.

**Conclusion:** Open-label preservative-free latanoprost eye drop emulsion treatment provided dual benefit of sustained IOP-lowering efficacy and improvements in OSD signs and symptoms over the 15-month study period. No serious treatment-related AEs were reported throughout the study period.

**Keywords:** corneal fluorescein staining, glaucoma, intraocular pressure, ocular surface disease, preservative-latanoprost eye drop emulsion, preserved latanoprost

## Introduction

Glaucoma represents a leading cause of irreversible sight loss, affecting approximately 3.6 million people aged 50 years and over worldwide.[1] Prevalence increases with age, and quality of life (QoL) diminishes with progressive deterioration of visual field.[1–4] From diagnosis, glaucoma is associated with increased incidence of anxiety, depression and other mental health and cognitive difficulties.[5–7] Elevated intraocular pressure (IOP) is the only known modifiable risk factor for disease progression and therapy typically aims to slow deterioration of visual field through the lowering of IOP.[2,8,9] The topical prostaglandin analog (PGA), latanoprost, is among the most widely-used IOP-lowering therapies

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recommended first-line for the treatment of open-angle glaucoma (OAG) and ocular hypertension (OHT).[2] Latanoprost monotherapy has demonstrated IOP-lowering efficacy in the treatment of OAG and OHT in numerous clinical studies.[10–15] However, chronic administration of topical glaucoma therapies may be associated with iatrogenic toxicity at the ocular surface and onset or worsening of ocular surface disease (OSD) in people with OAG/OHT.[16–27] Like OAG/OHT, OSD is associated with aging and prevalence is also known to be elevated further still among people living with glaucoma, compared with the general population.[17,19–25,28–33] Symptoms of OSD can negatively impact QoL among people with OAG/OHT and hamper adherence to treatment regimens as patients feel less able tolerate their topical medications, which may reduce persistence and affect long-term therapeutic outcomes.[2,18,26–28,33–37] Evidence suggests that holistic approaches to OAG/OHT management that aim to reduce OSD and tackle tolerability issues can help to enhance adherence and treatment persistence, resulting in improvements in IOP control and related outcomes (including vision-related QoL).[25,34,38,39]

European glaucoma guidelines recommend the use of preservative-free topical therapies to reduce OSD in patients who do not tolerate eye drops containing preservatives and in those on long-term therapy.[2] Studies have demonstrated non-inferiority concerning IOP-lowering efficacy with preservative-free latanoprost compared with preserved latanoprost formulations, but there remains a need for PGA monotherapies that address the signs and symptoms of OSD.[40–44] The preservative-free latanoprost 0.005% eye drop cationic emulsion comprises an oil-in-water formulation that aims to restore tear film stability and improve OSD signs and symptoms, while providing effective IOP reduction in OAG/OHT patients.[45–50] Once instilled, the cationic emulsion formulation helps to stabilize the tear film while delivering latanoprost directly to the ocular surface.[46,47] Phase III data from an international study demonstrated that this new latanoprost formulation provided effective IOP-lowering efficacy and improvements in OSD signs and symptoms at 12 weeks.[51] The Phase III trial comprised a 12-week, randomized, investigator-masked period followed by a 12-month open-label extension period.[51] Outcomes have been reported for the 12-week, randomized period, which achieved the primary efficacy endpoint of non-inferiority for the change in IOP from baseline with preservative-free latanoprost eye drop emulsion treatment versus preserved latanoprost.[51] IOP was reduced from baseline by >8 mmHg in both treatment arms at Week 4 and maintained through Week 12.[51] Statistical significance was demonstrated for the between-group difference in peak (09:00 AM) IOP change from baseline at Week 12 with the preservative-free latanoprost eye drop emulsion (nominal $p$=0.023).[51] The between-group difference for the change from baseline in trough (4:00 PM) IOP did not reach statistical significance (nominal $p$=0.080).[51] OSD signs were also reduced during the randomized study, with the least square (LS) mean change from baseline in corneal fluorescein staining (CFS) score being greater with preservative-free latanoprost eye drop emulsion compared with preserved latanoprost ($p$<0.001).[51] The change in OSD symptom score was similar across groups at Week 12 ($p$=0.090).[51]

Here, we report results from the 12-month open-label extension period for the same Phase III study, examining long-term efficacy and safety outcomes in patients continuing preservative-free latanoprost eye drop emulsion treatment and in those patients who switched from preserved latanoprost to the preservative-free eye drop emulsion formulation at Week 12. The study therefore provides insights regarding treatment outcomes over a 15-month period for patients who used the preservative-free latanoprost eye drop emulsion during both the randomized and open-label periods. In addition, the current analysis provides data over a 12-month period for those patients who switched to the eye drop emulsion formulation at the start of the open-label extension.

## Material and Methods

A Phase III, prospective, multicenter, multinational, 15-month study was conducted at 47 centers in Austria, Belgium, Estonia, Finland, France, Germany, Italy, Latvia, Poland, Spain, the United Kingdom, Russia and South Korea (EudraCT: 2017–004262-95). The study protocol was approved by the relevant Independent Ethics Committee for each study site and participating patients gave written informed consent. The trial was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation (ICH) E6 Good Clinical Practice (GCP) guideline.

The study comprised a 12-week parallel, randomized, investigator-masked, active-controlled, non-inferiority period, followed by a 12-month open-label extension (Figure 1). The methodology used for the 12-week randomized period has

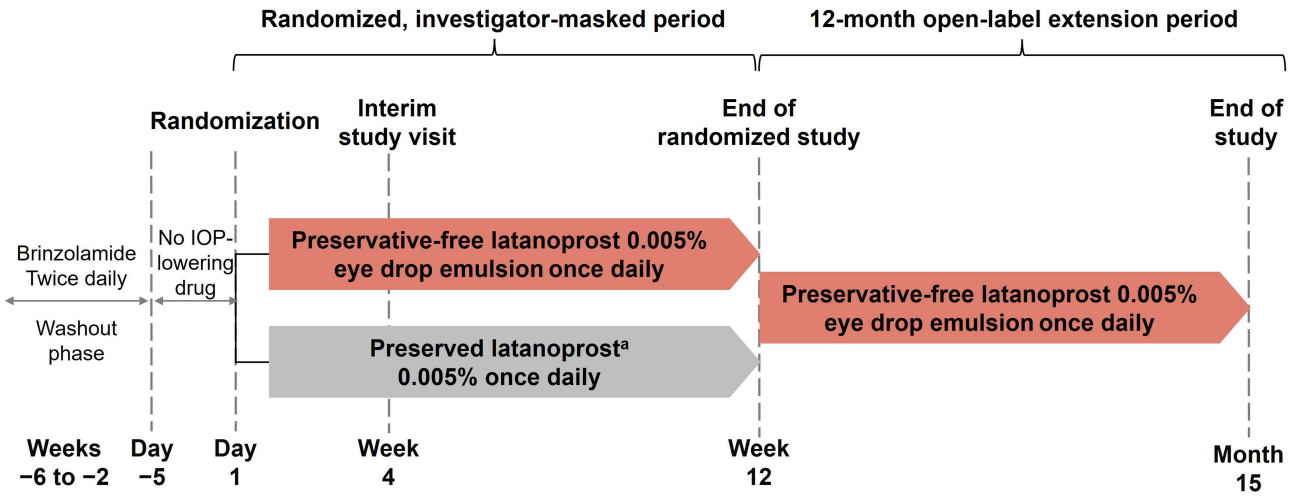


**Figure 1** Study design.
**Notes**: All patients were treated with preservative-free latanoprost 0.005% eye drop emulsion during the open-label extension period (Week 12 through Month 15).
[a]Preserved latanoprost was stipulated as the reference drug by the regulatory authorities.
**Abbreviation**: IOP, intraocular pressure.

already been described in detail by Baudouin et al (2024).[51] However, a brief summary is provided below for context alongside the methodology used for the open-label extension period reported in the current paper.

## Patient Population

Adults (aged ≥18 years) diagnosed with OAG/OHT and currently treated with topical IOP-lowering monotherapy were included in the study. Patients were required to have a stable visual field (≥6 months) and pre-washout IOP ≤18 mmHg in each eye. Post-washout IOP had to be ≥22 mmHg (≥1 eye) and ≤32 mmHg (both eyes). Patients were excluded if they had received treatment for glaucoma with a fixed-combination therapy, >1 topical therapy or an oral drug for glaucoma (within 6 months), or if they had undergone intraocular/filtering surgery. Other exclusion criteria were the presence of corneal abnormalities, significant visual field loss (during the previous year), optic nerve abnormality, severe blepharitis and/or meibomian gland disease, active ocular infection or severe dry eye disease (CFS score ≥4 on the modified Oxford scale; 0–V).[52] Pregnant or breastfeeding women were not allowed to enter the study.

## Study Treatment

Washout was conducted for between 5 days and 6 weeks, depending on the IOP-lowering therapy used prior to enrolment, during which patients used brinzolamide (10 mg/mL; one drop twice daily). Patients received no IOP-lowering therapy for 5 days prior to randomization.

At baseline (randomized period Day 1), patients were randomized 1:1 to receive one drop daily (in the evening) of either preservative-free latanoprost 0.005% eye drop cationic emulsion (Catiolanze®, Santen Oy, Tampere, Finland) or preserved latanoprost 0.005% solution (Xalatan®, Pfizer, Kent, UK). At Week 12, patients who completed the randomized period (in either treatment arm) were able to enter the extension period, during which they received open-label preservative-free latanoprost 0.005% eye drop emulsion treatment for a further 12 months, with follow up at Months 6, 9 and 15.

## Efficacy and Safety Endpoints and Assessments

The primary efficacy endpoint for the study (reported by Baudouin et al, 2024) was the change from baseline in peak (9:00 AM ± 1 hour) and trough (4:00 PM ± 1 hour) IOP (measured using Goldmann applanation tonometry) at Week 12 during the randomized period.[51] The non-inferiority margin was ≤1.5 mmHg 95% confidence interval for between-arm treatment difference.[51]


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Endpoints assessed during the open-label period at Week 12 and at Months 6, 9 and 15 included the change from baseline in peak (9:00 AM ± 1 hour) IOP, the CFS score (modified Oxford scale; 0–V) and the change from baseline in mean CFS score for patients with baseline CFS scores ≥1. Complete corneal clearing was defined as having a CFS score of 0. The change in mean OSD symptom score was assessed as the average of 3 symptoms: dry eye sensation, blurred/poor vision, and burning/stinging/itching (post-hoc analysis; defined for the primary analysis in the statistical analysis plan). Ocular symptom severity was graded using a 5-point scale: 0 (absent), 1 (mild), 2 (moderate), 3 (severe), 4 (very severe).

Tear break up time (TBUT) was measured in each eye at study visits using non-preserved 2% sodium fluorescein (2 μL instilled onto the bulbar conjunctiva using a micro-pipette). TBUT values were reported in seconds (s) as the average taken from two or three measurements. Slit lamp assessments for conjunctival hyperemia severity were conducted using a photographic scale derived from McMonnies scale (1–6).

Patient global rating of treatment was reported at Month 15, with patients selecting one of the following 4 choices relating to their experience with preservative-free latanoprost eye drop emulsion therapy: unsatisfactory, not very satisfactory, satisfactory, very satisfactory. Safety was assessed at all study visits and endpoints included changes in best-corrected distance visual acuity (BCDVA) and adverse events (AEs).

## Statistical Analysis

Statistical Analysis Software® (SAS) version 9.4 was used for all analyses. Randomization at baseline (randomized period Day 1) was stratified according to CFS score in the study eye (CFS ≤1 or CFS ≥2; modified Oxford scale). The full analysis set (FAS) included all patients in the randomized period (baseline through Week 12) who had received ≥1 dose of study medication and had ≥1 post-baseline IOP measurement. For the primary analysis, FAS recruitment aimed to reach 380 subjects (190 per treatment arm) in order to provide 90% power for the demonstration of non-inferiority. The open-label population comprised the first 130 FAS patients (and some additional patients from Belgium with informed consent) who completed their Week 12 visit at the end of the randomized period and received ≥1 dose of open-label preservative-free latanoprost eye drop emulsion and had ≥1 morning IOP measurement after Week 12. The open-label safety population comprised all patients from the open-label population who received 1 dose of study medication during the open-label period, regardless of whether they had a post-Week 12 IOP measurement. Analyses compared outcomes for patients in the open-label extension study based on their treatment group during the randomized study period; the preservative-free latanoprost eye drop emulsion group versus the preserved latanoprost group. Nominal p-values for between-group differences at Week 12 were calculated using a *t*-test and values below 0.05 were considered statistically significant.

# Results

In total, 384 patients (192 in each treatment arm) were included in the efficacy analysis during the 12-week randomized, investigator-masked period. Overall, 137 patients who completed the randomized period enrolled in the open-label extension study and were included in the open-label safety population (Figure 2). The open-label population included 136 patients; 70 patients had received preservative-free latanoprost eye drop emulsion treatment during the randomized period and 66 patients had been treated with preserved latanoprost solution. Four patients in each group discontinued prematurely during the open-label period and 129 completed the study (67 patients who received the preservative-free latanoprost eye drop emulsion during the randomized period and 62 who had used preserved latanoprost). A similar proportion of the open-label population completed the study in each group, 95.7% (prior preservative-free latanoprost eye drop emulsion use) and 93.9% (prior preserved latanoprost use) and discontinuations were deemed unlikely to significantly affect the validity of the analysis. Table 1 shows baseline (randomized period Day 1, post-washout) patient demographics and characteristics for the open-label population. Mean (standard deviation [SD]) age was 63.6 (10.5) years (range: 24–82 years). Most participants were female (61.8%) and White (97.8%). Patients were typically diagnosed with primary open-angle glaucoma (POAG; 74.3%) and OHT (23.5%), and the majority (71.9%) had been treated with PGA monotherapy prior to study entry.

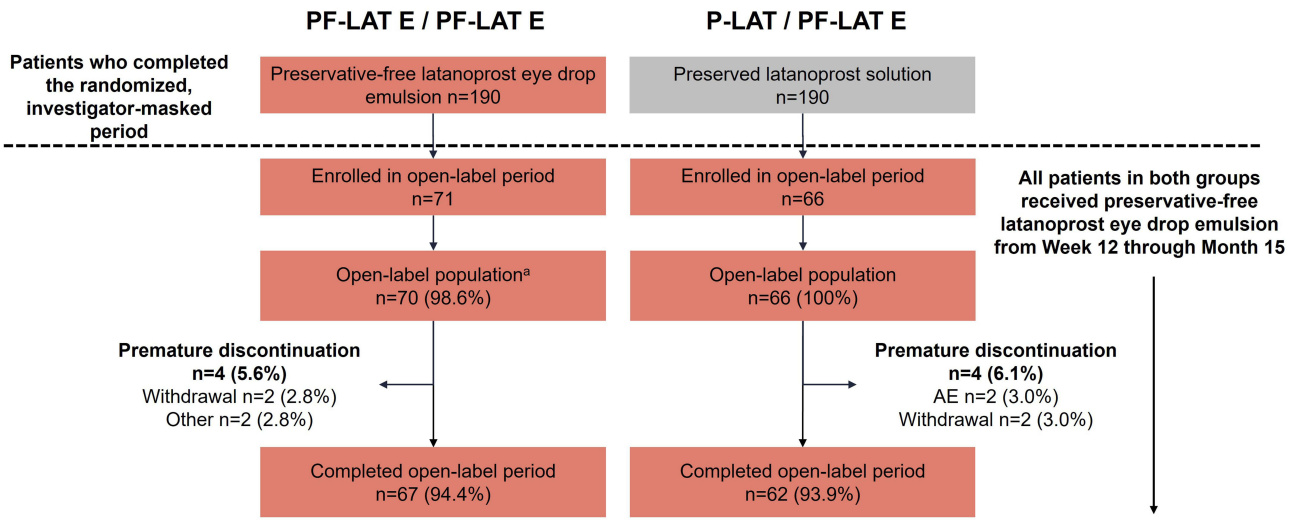


**Figure 2** Patient disposition chart.
**Notes**: [a]One patient was excluded from the open-label population due to the absence of a morning IOP measurement. The open-label safety population included all patients who enrolled in the open-label period and received at least one dose of study treatment, regardless of whether an IOP measurement was recorded. Treatment groups: PF-LAT E/PF-LAT E received preservative-free latanoprost 0.005% eye drop emulsion during both the randomized (baseline through Week 12) and open-label (Week 12 through Month 15) study periods. P-LAT/PF-LAT E received preserved latanoprost 0.005% during the randomized period (baseline through Week 12) and preservative-free latanoprost 0.005% eye drop emulsion during the open-label extension period (Week 12 through Month 15).
**Abbreviations**: AE, adverse event; IOP, intraocular pressure; PF-LAT E, preservative-free latanoprost eye drop emulsion; P-LAT, preserved latanoprost.

At baseline, data for those patients included in the open-label population showed that mean (SD) peak IOP was 24.3 (2.1) mmHg and 23.9 (1.7) mmHg for patients in the preservative-free latanoprost eye drop emulsion and preserved latanoprost groups, respectively. Mean (SD) CFS score at baseline was 0.8 (0.7) and 0.8 (0.8) in the preservative-free latanoprost eye drop emulsion and preserved latanoprost groups, respectively. Mean (SD) OSD symptom severity score was 0.8 (0.5) in both groups.

## IOP-Lowering

At Week 12, patients in the open-label population who had been treated with preservative-free latanoprost eye drop emulsion during the randomized period demonstrated a mean (SD) reduction in peak IOP from baseline of 8.9 (3.0) mmHg, compared with 7.8 (2.6) mmHg for those patients treated with preserved latanoprost (between-group difference: –1.06; nominal $p$=0.029; Figure 3). Patients using the preservative-free eye drop emulsion during both the randomized and open-label periods demonstrated mean (SD) reductions in peak IOP from baseline of 8.9 (3.0) mmHg, 9.0 (2.7) mmHg and 8.7 (2.3) mmHg at Months 6, 9 and 15, respectively. Patients who switched from preserved latanoprost at Week 12 showed respective IOP reductions of 8.3 (2.6) mmHg, 8.1 (2.7) mmHg and 7.6 (2.8) mmHg at Months 6, 9 and 15.

## OSD Improvement

Overall, 47.8% of the open-label population had baseline (randomized period Day 1) CFS scores ≥1. The mean (SD) reduction in CFS score at Week 12 was 0.6 (0.8) in the preservative-free latanoprost eye drop emulsion group and 0.4 (0.7) in the preserved latanoprost group.

Mean CFS score was reduced from baseline in both treatment groups in the open-label population through Month 15 (Figure 4). During the open-label period, patients who switched from preserved latanoprost at Week 12 to the preservative-free latanoprost eye drop emulsion demonstrated further reductions in CFS score so that the change from baseline was similar in both groups at Month 15. The mean (SD) reduction in CFS score from baseline at Month 15 was 0.7 (0.8) in the preservative-free latanoprost eye drop emulsion group and 0.8 (0.7) in the prior preserved latanoprost group. The proportion of patients with CFS 0 scores at baseline, Week 12 and Month 15 was 30.0%, 47.1% and 50.0%, respectively, in the group using the preservative-free latanoprost eye drop emulsion during both the randomized and


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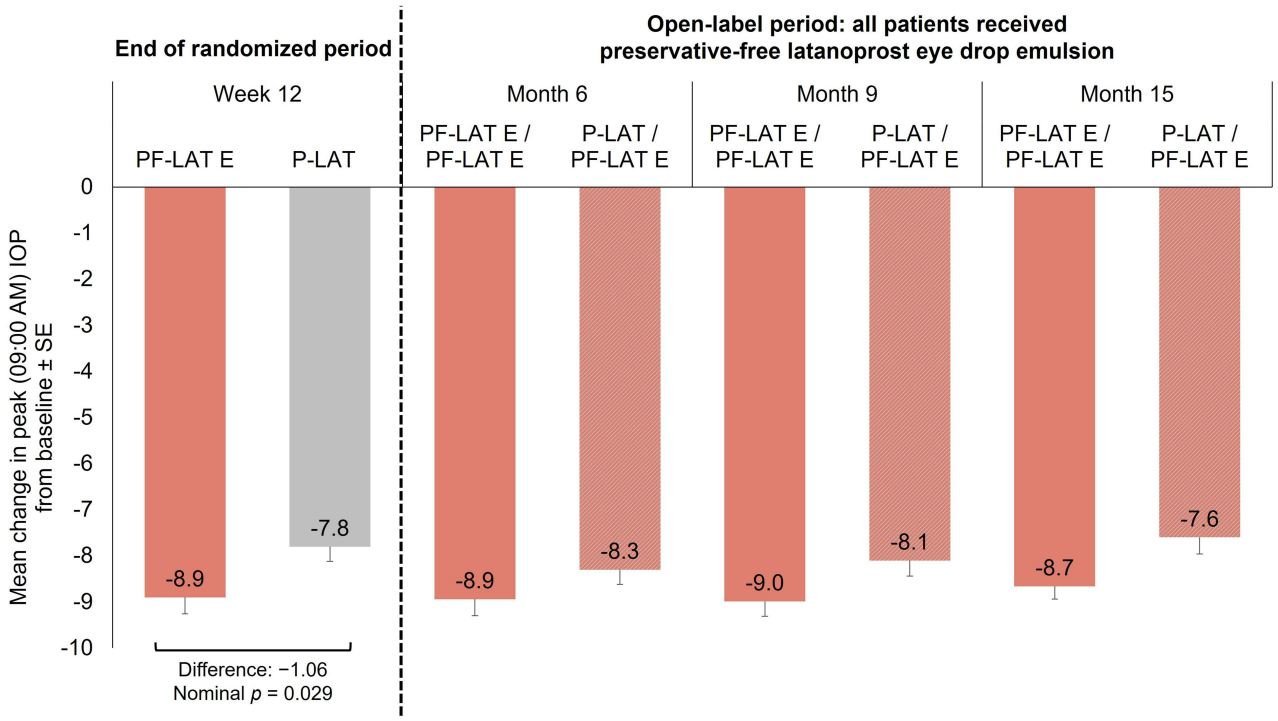
**Table 1** Baseline Characteristics of Patients Included in the Open-Label Population

| Characteristic | PF-LAT E/PF-LAT E (N=70) | P-LAT/PF-LAT E (N=66) | Overall (N=136) |
|---|---|---|---|
| Age, years | | | |
| Mean (SD) | 62.8 (10.62) | 64.6 (10.37) | 63.6 (10.50) |
| Minimum, maximum | 24, 82 | 35, 82 | 24, 82 |
| Sex, n (%) | | | |
| Male | 26 (37.1%) | 26 (39.4%) | 52 (38.2%) |
| Female | 44 (62.9%) | 40 (60.6%) | 84 (61.8%) |
| Ethnicity, n (%) | | | |
| White | 70 (100.0%) | 63 (95.5%) | 133 (97.8%) |
| Asian | 0 | 2 (3.0%) | 2 (1.5%) |
| Other | 0 | 1 (1.5%) | 1 (0.7%) |
| Primary diagnosis, n (%) | | | |
| POAG | 50 (71.4%) | 51 (77.3%) | 101 (74.3%) |
| PEX | 1 (1.4%) | 1 (1.5%) | 2 (1.5%) |
| Pigmentary glaucoma | 1 (1.4%) | 0 | 1 (0.7%) |
| OHT | 18 (25.7%) | 14 (21.2%) | 32 (23.5%) |
| Time since diagnosis, mean (SD), years | 5.3 (4.5) | 6.6 (5.9) | 5.9 (5.3) |
| Baseline IOP-lowering medication, n (%)[a] | | | |
| PGAs | 52 (74.3%) | 45 (69.2%) | 97 (71.9%) |
| CAIs | 11 (15.7%) | 7 (10.8%) | 18 (13.3%) |
| Beta-blockers | 4 (5.7%) | 9 (13.8%) | 13 (9.6%) |
| IOP (mmHg) | | | |
| Peak (9:00 AM ± 1 hour), mean (SD) | 24.3 (2.1) | 23.9 (1.7) | 24.1 (1.9) |
| Diurnal, mean (SD) | 23.9 (1.8) | 23.7 (1.3) | 23.8 (1.6) |
| CFS score (modified Oxford scale) | | | |
| Mean (SD)[b] | 0.8 (0.7) | 0.8 (0.8) | 0.8 (0.8) |
| CFS grade (modified Oxford scale), n (%) | | | |
| 0 | 21 (30.0%) | 20 (30.3%) | 41 (30.1%) |
| 0.5 | 16 (22.9%) | 14 (21.2%) | 30 (22.1%) |
| 1 | 20 (28.6%) | 21 (31.8%) | 41 (30.1%) |
| 2 | 12 (17.1%) | 8 (12.1%) | 20 (14.7%) |
| 3 | 1 (1.4%) | 3 (4.5%) | 4 (2.9%) |
| OSD symptom score | | | |
| Baseline score >0, n (%) | 37 (52.9) | 39 (59.1) | 76 (55.9) |
| Mean (SD) score | 0.8 (0.5) | 0.7 (0.5) | 0.7 (0.5) |
| TBUT ≤10 s | 45 (64.3) | 47 (71.2) | 92 (67.6) |

**Notes**: [a]Other prior IOP therapies were combinations of the listed medications. [b]There were no patients with a CFS score of 4 or 5. Treatment groups: PF-LAT E/PF-LAT E: received preservative-free latanoprost 0.005% eye drop emulsion during both the randomized (baseline through Week 12) and open-label study periods (Week 12 through Month 15). P-LAT/PF-LAT E: received preserved latanoprost 0.005% during the randomized period (baseline through Week 12) and preservative-free latanoprost 0.005% eye drop emulsion during the open-label extension period (Week 12 through Month 15).

**Abbreviations**: CAI, carbonic anhydrase inhibitor; CFS, corneal fluorescein staining; IOP, intraocular pressure; OHT, ocular hypertension; PEX, pseudo exfoliative glaucoma; PF-LAT E, preservative-free latanoprost eye drop emulsion; PGA, prostaglandin analog; P-LAT, preserved latanoprost; s, seconds; SD, standard deviation; TBUT, tear break up time.

open-label periods (Supplementary Figure S1). Overall, 30.3%, 40.9% and 48.4% of patients in the group switching from preserved latanoprost at the end of the randomized period demonstrated CFS 0 scores at baseline, Week 12 and Month 15, respectively. The proportion of patients with CFS scores ≥2 reduced from baseline in both treatment groups at Week 12 and Month 15. CFS scores ≥2 were seen in 18.5% (baseline), 5.7% (Week 12) and 2.9% (Month 15) of patients treated




| | Mean (SD) IOP, mmHg | | | | |
|---|---|---|---|---|---|
| | Baseline | Week 12 | Month 6 | Month 9 | Month 15 |
| PF-LAT E / PF-LAT E (N=70) | 24.3 (2.1) | 15.4 (2.6) | 15.3 (2.5) | 15.3 (2.5) | 15.6 (1.9) |
| P-LAT / PF-LAT E (N=66) | 23.9 (1.7) | 16.1 (2.9) | 15.7 (2.6) | 15.8 (2.8) | 16.4 (2.7) |

**Figure 3** Mean change in peak (9:00 AM) IOP from baseline in the open-label population.
**Notes**: All patients were treated with preservative-free latanoprost 0.005% eye drop emulsion during the open-label extension period (Week 12 through Month 15). Nominal p-value calculated using *t*-test. Treatment groups: PF-LAT E/PF-LAT E received preservative-free latanoprost 0.005% eye drop emulsion during both the randomized (baseline through Week 12) and open-label (Week 12 Through Month 15) study periods. P-LAT/PF-LAT E received preserved latanoprost 0.005% during the randomized period (baseline through Week 12) and preservative-free latanoprost 0.005% eye drop emulsion during the open-label extension period (Week 12 through Month 15). Between-group difference: preservative-free latanoprost eye drop cationic emulsion group – preserved latanoprost eye drop group. Nominal p-value calculated using *t*-test.
**Abbreviations**: IOP, intraocular pressure; PF-LAT E, preservative-free latanoprost eye drop emulsion; P-LAT, preserved latanoprost; SD, standard deviation; SE, standard error.

with preservative-free latanoprost eye drop emulsion during the randomized and open-label periods, and in 16.6% (baseline), 12.1% (Week 12) and 1.6% (Month 15) of those switching from preserved latanoprost.

Mean OSD symptom score (for patients with scores >0 at baseline) was reduced from baseline in both treatment groups at the end of the randomized period and continued to decrease through Month 15 (Figure 5). At Week 12, the mean (SD) reduction from baseline in OSD symptom score was 0.4 (0.4) and 0.2 (0.4) in the preservative-free latanoprost eye drop emulsion group and preserved latanoprost group, respectively. The mean (SD) reduction in OSD symptom score at Month 15 was 0.5 (0.4) in the preservative-free latanoprost eye drop emulsion group and 0.4 (0.4) in the prior preserved latanoprost group. When examining severity scores for individual OSD symptoms, a similar pattern of reduction from baseline was seen in the open-label population for both groups from Week 12 through Month 15 for burning/stinging/itching, dry eye and blurred/poor vision (Supplementary Table S1).

Mean (SD) TBUT was 5.2 (2.7) s at baseline and 7.1 (3.7) s at Month 15 with preservative-free latanoprost cationic eye drop emulsion. Patients switching from preserved latanoprost at Week 12 had TBUT values of 6.4 (2.7) s at baseline and 7.8 (3.8) s at Month 15. Conjunctival hyperemia outcomes were broadly similar between groups throughout the 15-month study period. At Month 15, the percentage of patients who rated preservative-free latanoprost eye drop emulsion treatment as satisfactory or very satisfactory was 100% for those who received this therapy during both the randomized and open-label periods and 98.4% for those who switched from preserved latanoprost.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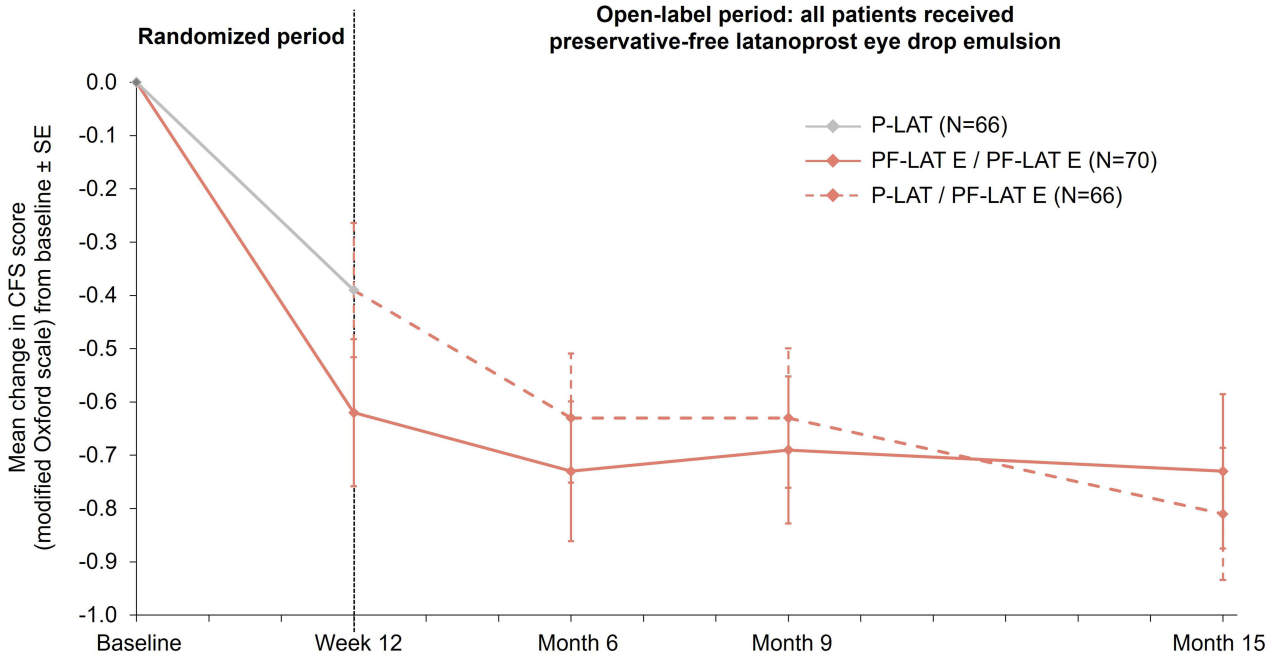



| | Mean (SD) CFS score (modified Oxford scale) | | | | |
|---|---|---|---|---|---|
| | Baseline | Week 12 | Month 6 | Month 9 | Month 15 |
| PF-LAT E / PF-LAT E (N=70) | 1.4 (0.6) | 0.8 (0.6) | 0.7 (0.6) | 0.8 (0.6) | 0.7 (0.5) |
| P-LAT / PF-LAT E (N=66) | 1.4 (0.7) | 1.1 (0.6) | 0.8 (0.5) | 0.8 (0.5) | 0.7 (0.4) |

**Figure 4** Mean change from baseline in CFS score (modified Oxford scale) for patients with baseline CFS scores ≥1 (open-label population).
**Notes**: All patients were treated with preservative-free latanoprost 0.005% eye drop emulsion during the open-label extension period (Week 12 through Month 15). Treatment groups: PF-LAT E/PF-LAT E received preservative-free latanoprost 0.005% eye drop emulsion during both the randomized (baseline through Week 12) and open-label (Week 12 through Month 15) study periods. The number of PF-LAT E/PF-LAT E patients with CFS ≥1 at baseline and included in the analysis was 33 at baseline, Week 12 and Month 6 and 32 at Months 9 and 15. P-LAT/PF-LAT E received preserved latanoprost 0.005% during the randomized period (baseline through Week 12) and preservative-free latanoprost 0.005% eye drop emulsion during the open-label extension period (Week 12 through Month 15). The number of P-LAT/PF-LAT E patients with CFS ≥1 at baseline and included in the analysis was 32 at baseline, Week 12 and Month 6 and 31 at Months 9 and 15.
**Abbreviations**: CFS, corneal fluorescein staining; PF-LAT E, preservative-free latanoprost eye drop emulsion; P-LAT, preserved latanoprost; SD, standard deviation; SE, standard error.

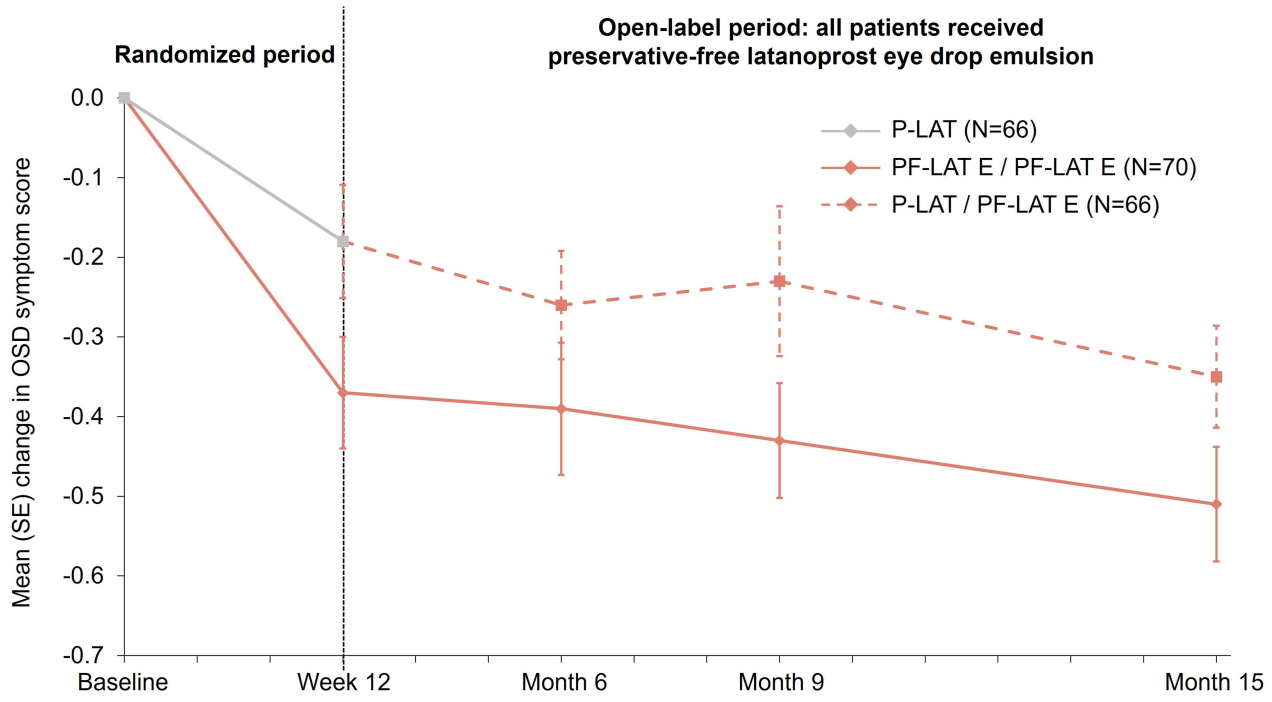
## Safety Endpoints

Slit lamp examinations at Week 12 and at Months 6, 9 and 15 showed no clinically meaningful changes from baseline in conjunctiva chemosis, lid and lid margin erythema or swelling, meibomian glands or tear film debris. No clinically relevant changes were observed regarding change in BCDVA from baseline at Month 6, 9 or 15.

In the open-label safety population, AEs were reported by 21 patients (29.6%) in the preservative-free latanoprost eye drop emulsion group and 21 patients (31.8%) in the prior preserved latanoprost group. Overall, 13 patients (9.5%) reported mild or moderate treatment-related AEs during the open-label period; 6 patients (8.5%) in the preservative-free latanoprost eye drop emulsion group and 7 (10.6%) in the prior preserved latanoprost group. All treatment-related AEs were ocular events (Table 2). Ocular hyperemia was the most common treatment-related AE, occurring in 2 patients in each group. One patient in the prior preserved latanoprost group discontinued due to a treatment-related AE (abnormal sensation in eye) during the open-label period. No serious treatment-related AEs were reported during the 12-month open-label extension study period.

# Discussion

Open-label preservative-free latanoprost eye drop cationic emulsion therapy provided durable IOP-lowering efficacy and good tolerability outcomes in patients with OAG/OHT participating in this international, Phase III study. Patients who




| | Mean (SD) OSD symptom score | | | | |
|---|---|---|---|---|---|
| | **Baseline** | **Week 12** | **Month 6** | **Month 9** | **Month 15** |
| PF-LAT E / PF-LAT E (N=70) | 0.8 (0.5) | 0.4 (0.4) | 0.4 (0.4) | 0.3 (0.3) | 0.3 (0.3) |
| P-LAT / PF-LAT E (N=66) | 0.7 (0.5) | 0.5 (0.5) | 0.4 (0.5) | 0.5 (0.5) | 0.3 (0.5) |

**Figure 5** Mean change from baseline in OSD symptom score for patients with scores >0 at baseline (open-label population; post-hoc analysis).
**Notes**: All patients were treated with preservative-free latanoprost 0.005% eye drop emulsion during the open-label extension period (Week 12 through Month 15). Treatment groups: PF-LAT E/PF-LAT E received preservative-free latanoprost 0.005% eye drop emulsion during both the randomized (baseline through Week 12) and open-label (Week 12 through Month 15) study periods. The number of PF-LAT E/PF-LAT E patients with OSD scores >0 at baseline and included in the analysis was 37 at baseline, Week 12, Month 6 and Month 9 and 36 at Month 15. P-LAT/PF-LAT E received preserved latanoprost 0.005% during the randomized period (baseline through Week 12) and preservative-free latanoprost 0.005% eye drop emulsion during the open-label extension period (Week 12 through Month15). The number of P-LAT/PF-LAT E patients with OSD scores >0 at baseline and included in the analysis was 39 at baseline, Week 12 and Month 6, 37 at Month 9 and 35 at Month 15. OSD symptom score comprised the average score for 3 symptoms: dry eye sensation, blurred/poor vision, and burning/stinging/itching.
**Abbreviations**: OSD, ocular surface disease; PF-LAT E, preservative-free latanoprost eye drop emulsion; P-LAT, preserved latanoprost; SD, standard deviation; SE, standard error.

used the preservative-free latanoprost eye drop emulsion formulation for the entire 15-month study period sustained reductions in peak (9:00 AM) IOP from baseline of ≥8.7 mmHg from Week 12 through Month 15. Patients switching

**Table 2** Treatment-Related Adverse Events in ≥1% of the 12-Month Open-Label Safety Population

| | **PF-LAT E/PF-LAT E** | **P-LAT/PF-LAT E** | **Overall** |
|---|---|---|---|
| | **(N=71)** | **(N=66)** | **(N=137)** |
| Any treatment-related AE, n (%) | 6 (8.5) | 7 (10.6) | 13 (9.5) |
| Eye disorders | 6 (8.5) | 6 (9.1) | 12 (8.8) |
| Ocular hyperaemia | 2 (2.8) | 2 (3.0) | 4 (2.9) |
| Abnormal sensation | 1 (1.4) | 2 (3.0) | 3 (2.2) |
| Conjunctival hyperaemia | 1 (1.4) | 1 (1.5) | 2 (1.5) |
| Growth of eyelashes | 1 (1.4) | 2 (3.0) | 3 (2.2) |

(*Continued*)


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**Table 2** (Continued).

| | PF-LAT E/PF-LAT E (N=71) | P-LAT/PF-LAT E (N=66) | Overall (N=137) |
|---|---|---|---|
| Eye paraesthesia | 1 (1.4) | 0 | 1 (0.7) |
| Blepharitis | 1 (1.4) | 0 | 1 (0.7) |
| Eyelid erythema | 0 | 1 (1.5) | 1 (0.7) |
| Eye pruritus | 0 | 1 (1.5) | 1 (0.7) |
| Swelling of eyelid | 0 | 2 (3.0) | 2 (1.5) |
| General disorders and administration site conditions | 0 | 1 (1.5) | 1 (0.7) |
| Instillation site pain | 0 | 1 (1.5) | 1 (0.7) |

**Notes**: All patients were treated with preservative-free latanoprost eye drop emulsion during the open-label extension period (Week 12 through Month 15). Treatment-related AEs were defined as any AEs that were considered related to a study drug, study procedure, or artificial tears by the investigator; no AEs related to study procedures or artificial tears were reported. Treatment groups: PF-LAT E/PF-LAT E: received preservative-free latanoprost 0.005% eye drop emulsion during both the randomized (baseline through Week 12) and open-label (Week 12 through Month 15) study periods. P-LAT/PF-LAT E: received preserved latanoprost 0.005% during the randomized period (baseline through Week 12) and preservative-free latanoprost 0.005% eye drop emulsion during the open-label extension period (Week 12 through Month 15).

**Abbreviations**: AE, adverse event; PF-LAT E, preservative-free latanoprost eye drop emulsion; P-LAT, preserved latanoprost.

from preserved latanoprost to the preservative-free latanoprost eye drop emulsion at Week 12 maintained peak IOP reductions from baseline of ≥7.6 mmHg throughout the 12-month open-label extension period. The between-group difference for the change from baseline in peak IOP was statistically significant at Week 12 (nominal $p$=0.029) for patients who were treated with preservative-free latanoprost eye drop emulsion during the randomized period, compared with patients using preserved latanoprost. Reductions in IOP were accompanied by ongoing improvements in the signs and symptoms of OSD through Month 15 and preservative-free latanoprost eye drop emulsion therapy was well-tolerated throughout the entire study period with no serious treatment-related AEs reported.

IOP reductions reported by Baudouin et al (2024) for the 12-week, randomized, investigator-masked period of the same study were maintained throughout the open-label period, regardless of whether patients had received preserved latanoprost or preservative-free latanoprost eye drop emulsion during the randomized period.[51] These results demonstrate the enduring IOP-lowering efficacy provided by the preservative-free latanoprost eye drop emulsion, and the magnitude of IOP reduction sustained over the 15-month study reflects previous long-term trials examining latanoprost monotherapy in OAG/OHT patients.[10,53,54] IOP remains the only proven risk factor for progressive visual deterioration in glaucoma and treatments that provide long-lasting IOP reduction may extend the length of time that patients are able to experience good levels of visual acuity and vision-related QoL.[2,6,8,9,39,55]

Debate continues regarding the likely impact of OSD on treatment outcomes in glaucoma.[2,8,9,23–25,27,29] However, the results from this Phase III study showed that patients who experienced the dual benefits of IOP-lowering efficacy and improvement in OSD signs and symptoms with the preservative-free eye drop emulsion formulation during the 12-week randomized period sustained those outcomes through Month 15.[51] The ongoing reduction in OSD signs (CFS score) observed in patients using the preservative-free latanoprost eye drop emulsion over a 15-month period and the additional improvement seen in patients who switched to the preservative-free eye drop emulsion from preserved latanoprost at Week 12 may have been due to the emulsion formulation helping to address issues at the ocular surface and/or could have resulted from preservative-related toxicities becoming less severe over time.[45–47,51] Patients switching to the preservative-free eye drop emulsion from preserved latanoprost at the start of the open-label period demonstrated further reductions in CFS score so that the change from baseline was comparable across groups at Month 15. The mechanisms underpinning the observed changes in CFS score with the new latanoprost formulation may warrant further investigation in future clinical studies. Both groups continued to show incremental reductions in OSD symptom score with open-label preservative-free latanoprost eye drop emulsion treatment throughout the extension, and previous studies have suggested that effective management of OSD in OAG/OHT patients can influence adherence with topical glaucoma therapy.[21,23–27,29] The improvements in OSD signs and symptoms demonstrated in the current study may have supported consistent adherence with the therapeutic regimen, which represents an ongoing challenge in the management of chronic conditions,

including glaucoma.[34,39] Future studies comparing parameters around adherence and QoL differences with the preservative-free eye drop emulsion formulation and preserved latanoprost would be of value to gain insights on any changes to compliance levels with these treatments. Current guidelines already highlight the importance of considering tolerability when selecting treatments for glaucoma.[2] A therapy that provides improvements in OSD signs and symptoms and QoL, while promoting better adherence, may support better long-term glaucoma outcomes in clinical practice.

During the randomized period, the percentage of patients rating treatment as satisfactory or very satisfactory was 98.4% in the preservative-free latanoprost eye drop emulsion group and 90.5% in the preserved latanoprost group.[51] During the open-label period, 100% of patients continuing preservative-free latanoprost eye drop emulsion treatment and 98.4% switching from preserved latanoprost rated their therapy to be satisfactory/very satisfactory.[51] Further investigations would be required to understand the reasons for high patient ratings during the entire study period, but these results indicate that patients found tolerability with the open-label study treatment to be acceptable. Overall, less than 10% of patients experienced AEs related to study treatment and no serious AEs were associated with preservative-free latanoprost eye drop emulsion use during the study. Treatment-related AEs reported during the study period reflected those of previous studies examining latanoprost monotherapy in OAG/OHT patients.[10,53,54]

Limitations of the current study include the relatively small sample size (136 patients in total) and the open-label design, which could have introduced reporting bias for some outcomes (particularly subjective symptom severity), and the analysis may have been susceptible to issues such as regression to the mean. In addition, the outcomes should be considered in the context of other potential factors, including the influence of placebo effect and improvements in tolerability due to washout of preservative agent over time in the prior preserved latanoprost group. Future studies would benefit from the robustness of a larger analysis population and control group, with investigator masking. However, the results from the current study provide an indication of the outcomes that clinicians may observe in their own practice. A comparison of treatment outcomes with the preservative-free latanoprost eye drop emulsion and other PGA treatments (eg bimatoprost, tafluprost) may also be of value.

## Conclusion

Results from the open-label extension to a Phase III study revealed the potential dual benefits of durable IOP-lowering efficacy and improvement in OSD signs and symptoms over a 15-month period in patients with OAG/OHT treated with the preservative-free latanoprost eye drop cationic emulsion. Patients switching to the emulsion formulation from preserved latanoprost at Week 12 maintained IOP outcomes over a 12-month period and experienced additional improvements in the signs and symptoms of OSD so that both groups demonstrated a similar change from baseline at Month 15. Treatment was well tolerated, and no serious AEs were associated with study medication. The outcomes provide the basis for larger randomized studies examining long-term OAG/OHT treatment with the preservative-free latanoprost eye drop cationic emulsion.

## Abbreviations

AE, adverse events; BCDVA, best-corrected distance visual acuity; CAI, carbonic anhydrase inhibitor; CFS, corneal fluorescein staining; FAS, Full Analysis Set; IOP, intraocular pressure; OAG, open-angle glaucoma; OHT, ocular hypertension; OSD, ocular surface disease; PEX, pseudo exfoliative glaucoma; PF-LAT E, preservative-free latanoprost eye drop emulsion; PGA, prostaglandin analog; P-LAT, preserved latanoprost; QoL, quality of life; s, seconds; SD, standard deviation; SE, standard error; TBUT, tear break up time.

## Data Sharing Statement

The study was registered on the European Union Clinical Trials Register (EudraCT: 2017-004262-95). Key data from the study are available via the EU Clinical Trials Register website or are available from the corresponding author upon reasonable request.

## Ethics Approval and Informed Consent

The study was performed after Independent Ethics Committee (IEC) approval. The protocol and amendments were reviewed and approved by the relevant IECs for each study site. Participating patients were required to give written

informed consent. The study was conducted in accordance with the Declaration of Helsinki and its most recent update, and the International Council for Harmonisation (ICH) E6 Good Clinical Practice (GCP) guideline.

## Consent for Publication

Patient consent was obtained for publication.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## References

1. Steinmetz JD, Bourne RRA, Briant PS, et al. Causes of blindness and vision impairment in 2020 and trends over 30 years, and prevalence of avoidable blindness in relation to VISION 2020: the Right to Sight: an analysis for the Global Burden of Disease Study. *Lancet Glob Health*. 2021;9(2):e144–e160. doi:10.1016/S2214-109X(20)30489-7
2. European Glaucoma Society. Terminology and guidelines for glaucoma. *Br J Ophthalmol*. 2021;105(Suppl 1):1–169. doi:10.1136/bjophthalmol-2021-egsguidelines.
3. Khachatryan N, Pistilli M, Maguire MG, et al. A Review of studies of the association of vision-related quality of life with measures of visual function and structure in patients with glaucoma in the United States. *Ophthalmic Epidemiol*. 2021;28(3):265–276. doi:10.1080/09286586.2020.1863992
4. Peters D, Heijl A, Brenner L, Bengtsson B. Visual impairment and vision-related quality of life in the Early Manifest Glaucoma Trial after 20 years of follow-up. *Acta Ophthalmol*. 2015;93(8):745–752. doi:10.1111/aos.12839
5. Latif K, Nishida T, Moghimi S, Weinreb RN. Quality of life in glaucoma. *Graefes Arch Clin Exp Ophthalmol*. 2023;261(10):3023–3030. doi:10.1007/s00417-023-06050-z
6. Quaranta L, Riva I, Gerardi C, Oddone F, Floriani I, Konstas AGP. Quality of life in glaucoma: a review of the literature. *Adv Ther*. 2016;33(6):959–981. doi:10.1007/s12325-016-0333-6
7. Arrigo A, Aragona E, Saladino A, et al. Cognitive dysfunctions in glaucoma: an overview of morpho-functional mechanisms and the impact on higher-order visual function. *Front Aging Neurosci*. 2021;13:1. doi:10.3389/fnagi.2021.747050
8. The AGIS Investigators. The advanced glaucoma intervention study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. *Am J Ophthalmol*. 2000;130(4):429–440. doi:10.1016/s0002-9394(00)00538-9.
9. International Council of Ophthalmology. Guidelines for glaucoma care. 2016. Available from: https://icoph.org/eye-care-delivery/glaucoma/. Accessed August 15, 2022.
10. Alm A. Latanoprost in the treatment of glaucoma. *Clin Ophthalmol*. 2014;8:1967–1985. doi:10.2147/OPTH.S59162
11. Camras CB. Comparison of latanoprost and timolol in patients with ocular hypertension and glaucoma. *Ophthalmology*. 1996;103(1):138–147. doi:10.1016/S0161-6420(96)30749-5
12. Alm A, Stjernschantz J. Effects on intraocular pressure and side effects of 0.005% latanoprost applied once daily, evening or morning. *Ophthalmology*. 1995;102(12):1743–1752. doi:10.1016/S0161-6420(95)30798-1
13. Alm A, Cb C, Pg W. Phase III latanoprost studies in Scandinavia, the United Kingdom and the United States. *Surv Ophthalmol*. 1997;41:S105–S110. doi:10.1016/S0039-6257(97)80016-1
14. Camras CB, Alm A, Watson P, et al. Latanoprost, a prostaglandin analog, for glaucoma therapy. *Ophthalmology*. 1996;103(11):1916–1924. doi:10.1016/S0161-6420(96)30407-7
15. Digiuni M, Fogagnolo P, Rossetti L. A review of the use of latanoprost for glaucoma since its launch. *Expert Opin Pharmacother*. 2012;13(5):723–745. doi:10.1517/14656566.2012.662219
16. Wolfram C, Stahlberg E, Pfeiffer N. Patient-reported nonadherence with glaucoma therapy. *J Ocul Pharmacol Ther*. 2019;35(4):223–228. doi:10.1089/jop.2018.0134
17. Asiedu K, Abu SL. The impact of topical intraocular pressure lowering medications on the ocular surface of glaucoma patients: a review. *J Curr Ophthalmol*. 2019;31(1):8–15. doi:10.1016/j.joco.2018.07.003

18. Pisella PJ, Pouliquen P, Baudouin C. Prevalence of ocular symptoms and signs with preserved and preservative free glaucoma medication. *Br J Ophthalmol*. 2002;86(4):418–423. doi:10.1136/bjo.86.4.418
19. Erb C, Gast U, Schremmer D. German register for glaucoma patients with dry eye. I. Basic outcome with respect to dry eye. *Graefes Arch Clin Exp Ophthalmol*. 2008;246(11):1593–1601. doi:10.1007/s00417-008-0881-9
20. Leung EW, Medeiros FA, Weinreb RN. Prevalence of ocular surface disease in glaucoma patients. *J Glaucoma*. 2008;17(5):350–355. doi:10.1097/IJG.0b013e31815c5f4f
21. Pérez-Bartolomé F, Martínez-de-la-Casa JM, Arriola-Villalobos P, Fernández-Pérez C, Polo V, García-Feijoó J. Ocular surface disease in patients under topical treatment for glaucoma. *Eur J Ophthalmol*. 2017;27(6):694–704. doi:10.5301/ejo.5000977
22. Garcia-Feijoo J, Sampaolesi JR. A multicenter evaluation of ocular surface disease prevalence in patients with glaucoma. *Clin Ophthalmol*. 2012;6:441–446. doi:10.2147/OPTH.S29158
23. Kaštelan S, Tomić M, Soldo K M, Salopek-Rabatić J. How ocular surface disease impacts the glaucoma treatment outcome. *Biomed Res Int*. 2013;2013:696328. doi:10.1155/2013/696328
24. Kolko M, Gazzard G, Baudouin C, et al. Impact of glaucoma medications on the ocular surface and how ocular surface disease can influence glaucoma treatment. *Ocul Surf*. 2023;29:456–468. doi:10.1016/j.jtos.2023.05.012
25. Mylla Boso AL, Gasperi E, Fernandes L, Costa VP, Alves M. Impact of Ocular Surface Disease treatment in patients with glaucoma. *Clin Ophthalmol*. 2020;14:103–111. doi:10.2147/OPTH.S229815
26. Nijm LM, Schweitzer J, Blackmore JG. Glaucoma and dry eye disease: opportunity to assess and treat. *Clin Ophthalmol*. 2023;17:3063–3076. doi:10.2147/OPTH.S420932
27. Nijm LM, De Benito-Llopis L, Rossi GC, Vajaranant TS, Coroneo MT. Understanding the dual dilemma of dry eye and glaucoma: an international review. *Asia Pac J Ophthalmol*. 2020;9(6):481–490. doi:10.1097/APO.0000000000000327
28. Li G, Akpek EK, Ahmad S. Glaucoma and ocular surface disease: more than meets the eye. *Clin Ophthalmol*. 2022;16:3641–3649. doi:10.2147/OPTH.S388886
29. Batra R, Tailor R, Mohamed S. Ocular surface disease exacerbated glaucoma. *J Glaucoma*. 2014;23(1):56–60. doi:10.1097/IJG.0b013e318264cd68
30. Voicu L, Salim S. New strategies for the management of ocular surface disease in glaucoma patients. *Curr Opin Ophthalmol*. 2021;32(2):134–140. doi:10.1097/ICU.0000000000000739
31. Ruiz-Lozano RE, Azar NS, Mousa HM, et al. Ocular surface disease: a known yet overlooked side effect of topical glaucoma therapy. *Front Toxicol*. 2023;5. doi:10.3389/ftox.2023.1067942
32. Zhou X, Zhang X, Zhou D, Zhao Y, Duan X. A narrative review of ocular surface disease related to anti-glaucomatous medications. *Ophthalmol Ther*. 2022;11(5):1681–1704. doi:10.1007/s40123-022-00557-0
33. Baudouin C, Kolko M, Melik-Parsadaniantz S, Messmer EM. Inflammation in glaucoma: from the back to the front of the eye, and beyond. *Prog Retin Eye Res*. 2021;83:100916. doi:10.1016/j.preteyeres.2020.100916
34. Tapply I, Broadway DC. Improving Adherence to Topical Medication in Patients with Glaucoma. *Patient Prefer Adherence*. 2021;15:1477–1489. doi:10.2147/PPA.S264926
35. Baudouin C. Detrimental effect of preservatives in eyedrops: implications for the treatment of glaucoma. *Acta Ophthalmol*. 2008;86(7):716–726. doi:10.1111/j.1755-3768.2008.01250.x
36. Jaenen N, Baudouin C, Pouliquen P, Manni G, Figueiredo A, Zeyen T. Ocular symptoms and signs with preserved and preservative-free glaucoma medications. *Eur J Ophthalmol*. 2007;17(3):341–349. doi:10.1177/112067210701700311
37. Aguayo Bonniard A, Yeung JY, Chan CC, Birt CM. Ocular surface toxicity from glaucoma topical medications and associated preservatives such as benzalkonium chloride (BAK). *Expert Opin Drug Metab Toxicol*. 2016;12(11):1279–1289. doi:10.1080/17425255.2016.1209481
38. Ansari E, Chappiti S, Pavicic-Astalos J, et al. Treatment of open-angle glaucoma and ocular hypertension with preservative-free tafluprost/timolol fixed-dose combination therapy: 6 case reports and clinical outcomes. *BMC Ophthalmol*. 2022;22(1):152. doi:10.1186/s12886-022-02361-7
39. Nordmann JP, Auzanneau N, Ricard S, Berdeaux G. Vision related quality of life and topical glaucoma treatment side effects. *Health Qual Life Outcomes*. 2003;75:1–9. doi:10.1186/1477-7525-1-75
40. Seong HJ, Lee K, Sj L, Kim S, Park JW. Efficacy and safety of preservative-free latanoprost eyedrops compared with preserved prostaglandin analogues in patients with open-angle glaucoma. *Korean J Ophthalmol*. 2021;35(3):235–241. doi:10.3341/kjo.2021.0010
41. Rouland JF, Traverso CE, Stalmans I, et al. Efficacy and safety of preservative-free latanoprost eyedrops, compared with BAK-preserved latanoprost in patients with ocular hypertension or glaucoma. *Br J Ophthalmol*. 2013;97(2):196–200. doi:10.1136/bjophthalmol-2012-302121
42. Aptel F, Choudhry R, Stalmans I. Preservative-free versus preserved latanoprost eye drops in patients with open-angle glaucoma or ocular hypertension. *Curr Med Res Opin*. 2016;32(8):1457–1463. doi:10.1080/03007995.2016.1202818
43. Chamard C, Larrieu S, Baudouin C, Bron A, Villain M, Daien V. Preservative-free versus preserved glaucoma eye drops and occurrence of glaucoma surgery. A retrospective study based on the French national health insurance information system, 2008-2016. *Acta Ophthalmol*. 2020;98(7):e876–e881. doi:10.1111/aos.14410
44. Kandarakis S, Papadopoulos AP, Roussopoulos G, et al. COMfort Eye Trial (COMET) results - a non-inferiority, randomized, investigator-masked, two-parallel group, phase III clinical trial, to evaluate the efficacy and safety of a preservative free formulation of latanoprost versus a reference drug (Xalatan®) in patients with primary open-angle glaucoma (POAG) or ocular hypertension (OHT). *Expert Opin Drug Saf*. 2024;23(6):743–754. doi:10.1080/14740338.2023.2252341
45. Daull P, Garrigue JS. Preservative-free cationic nanoemulsion of latanoprost. *Ophthalmol Times J*. 2013;2013:1–4.
46. Daull P, Amrane M, Garrigue JS. Novasorb® cationic nanoemulsion and latanoprost: the ideal combination for glaucoma management? *J Eye Dis Disord*. 2017;2017:1–4 doi:10.35248/2684-1622.17.2.107
47. Daull P, Garrigue JS, Liang H, Baudouin C. Use of a cationic emulsion of latanoprost to treat glaucoma patients with ocular surface disease: a preclinical review. *J Ocul Pharmacol Ther*. 2023;39(4):240–251. doi:10.1089/jop.2022.0155
48. Daull P, Buggage R, Lambert G, et al. A comparative study of a preservative-free latanoprost cationic emulsion (Catioprost) and a BAK-preserved latanoprost solution in animal models. *J Ocul Pharmacol Ther*. 2012;28(5):515–523. doi:10.1089/jop.2011.0245
49. Ismail D, Amrane M, Garrigue J-S, Buggage R. A Phase 2, randomized study evaluating the safety and efficacy of Catioprost® (unpreserved latanoprost 0.005% emulsion) compared to Travatan Z® in subjects with glaucoma and ocular surface disease. *Acta Ophthalmol*. 2011;89(s248). doi:10.1111/j.1755-3768.2011.227.x

50. Buggage R, Amrane M, Ismail D, Pisella PJ, Baudouin C. An Examination of the improvement in ocular surface disease (OSD) in glaucoma patients following 3 months of treatment with Catioprost®, a preservative-free latanoprost 0.005% cationic emulsion, in two multi-center studies. *European Glaucoma Society Congress*. 2012.
51. Baudouin C, Stalmans I, Bourne R, et al. A phase III study comparing preservative-free latanoprost eye drop emulsion with preserved latanoprost in open-angle glaucoma or ocular hypertension. *Eye (Lond)*. 2025;39(8):1599–1607. doi:10.1038/s41433-025-03646-z
52. Bron AJ, Evans VE, Smith JA. Grading of corneal and conjunctival staining in the context of other dry eye tests. *Cornea*. 2003;22(7):640–650. doi:10.1097/00003226-200310000-00008
53. Alm A, Widengård I. Latanoprost: experience of 2-year treatment in Scandinavia. *Acta Ophthalmol Scand*. 2000;78(1):71–76. doi:10.1034/j.1600-0420.2000.078001071.x
54. Hedman K, Watson PG, Alm A. The effect of latanoprost on intraocular pressure during 2 years of treatment. *Surv Ophthalmol*. 2002;47(1):S65–76. doi:10.1016/s0039-6257(02)00301-6
55. Nelson P, Aspinall P, Papasouliotis O, Worton B, O'Brien C. Quality of life in glaucoma and its relationship with visual function. *J Glaucoma*. 2003;12(2):139–150. doi:10.1097/00061198-200304000-00009