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A Randomized, Controlled Comparison of NCX 470 (0.021%, 0.042%, and 0.065%) and Latanoprost 0.005% in Patients With Open-angle Glaucoma or Ocular Hypertension: The Dolomites Study

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Précis: NCX 470 0.042% and 0.065% were statistically superior in intraocular pressure (IOP) lowering to latanoprost 0.005%, and NCX 470 0.021% was noninferior. All NCX 470 concentrations were safe and well tolerated.

Purpose: The purpose of this study was to compare varying concentrations of NCX 470 (a nitric oxide–donating bimatoprost) to latanoprost in a dose-response safety and efficacy trial.

Patients and Methods: Adult patients with bilateral open-angle glaucoma or ocular hypertension were randomized to NCX 470 0.021% (n = 111), 0.042% (n = 108), 0.065% (n = 107), or latanoprost 0.005% (n = 107) once daily in the evening. IOP was measured at 8:00 AM, 10:00 AM, and 4:00 PM at weeks 1, 2, and 4. The primary efficacy endpoint was the reduction from baseline in mean diurnal IOP at week 4. Secondary efficacy endpoints included reductions from baseline in mean diurnal IOP at weeks 1 and 2, and reductions from baseline in time-matched IOP at 8:00 AM, 10:00 AM, and 4:00 PM at weeks 1, 2, and 4. Adverse events were evaluated.

Results: All concentrations of NCX 470 resulted in significant reductions of mean diurnal IOP. The 0.042% and 0.065% concentrations were statistically superior to latanoprost 0.005%, and 0.021% was noninferior to latanoprost for change from baseline in mean diurnal IOP at week 4. The 0.065% concentration was also superior to latanoprost by up to 1.4 mm Hg for reduction from baseline at 8:00 AM, 10:00 AM, and 4:00 PM at week 4. NCX 470 was safe and well tolerated; conjunctival hyperemia was the most frequently reported adverse event.

Conclusions: NCX 470 demonstrated dose-dependent reductions in IOP. The 0.042% and 0.065% concentrations demonstrated significantly greater reductions from baseline in mean diurnal IOP than latanoprost 0.005% at week 4, suggesting that higher concentrations may show even greater efficacy.

Key Words: NCX 470, nitric oxide, open-angle glaucoma, ocular hypertension, intraocular pressure

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Glaucoma is a leading cause of blindness worldwide.[1] Globally, it has been estimated that 64.3 million people (aged 40–80 y) were affected by glaucoma in 2013, with this number projected to rise to 111.8 million in 2040.[2] Elevated intraocular pressure (IOP) is the primary risk factor for glaucoma, and lowering IOP to prevent optic nerve injury is currently the only proven effective treatment.[1] According to the Early Manifest Glaucoma Trial (EMGT), every 1 mm Hg of IOP lowering further reduced the risk of glaucomatous progression.[3] Topical prostaglandin analogues (PGAs) have become the mainstay of initial medical treatment due to their efficacy and safety in lowering IOP.[4] Generic latanoprost is the most commonly prescribed PGA although clinical trials reported a greater reduction in IOP in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT) with bimatoprost 0.03% compared with either travoprost 0.004% or latanoprost 0.005% in some instances.[5] Other studies report equivalence among the 3 treatments.[6,7] To the best of our knowledge, no single agent IOP-lowering therapy has been demonstrated to be superior to latanoprost in a large clinical trial.

Nitric oxide (NO)-donating PGAs have been proposed to improve IOP-lowering efficacy over PGA alone. The first approved NO donor, and prostaglandin F2α receptor agonist is latanoprostene bunod 0.024%, dual-acting NO-donating latanoprost developed for the reduction of IOP in patients with OAG or OHT. While a small phase 2 trial suggested superiority to latanoprost, the registration trials and basis for approval was the demonstration that latanoprostene bunod ophthalmic solution, 0.024% was noninferior to timolol maleate ophthalmic solution, 0.5% in patients with OAG or OHT.[8,9]

NCX 470, is a NO-donating bimatoprost, with chemical name hexanoic acid, 6-(nitrooxy)-, (1S,2E)-3-[(1R,2R,3S,5R)-2-[(2Z)-7-(ethylamino)-7-oxo-2-hepten-1-yl]-3,5-dihydroxycyclopentyl]-1-(2-phenylethyl)-2-propen-1-yl ester. NCX 470 is being developed as a new therapy for lowering IOP in patients with OAG or OHT (Fig. 1). When exposed to esterases in the eye, NCX 470 is cleaved into its active

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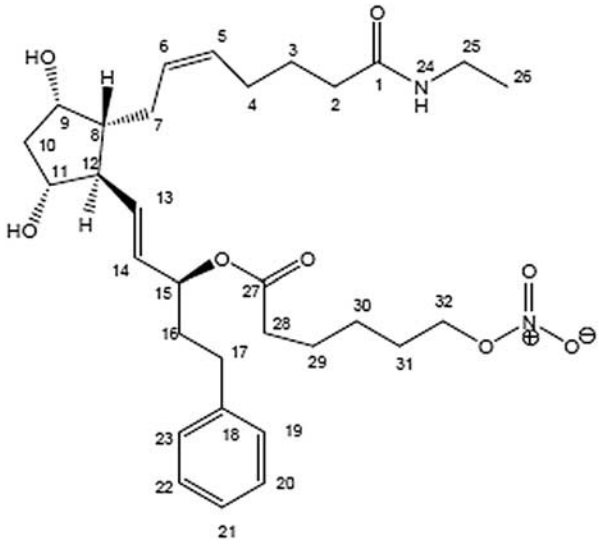

FIGURE 1. Chemical structure of NCX 470.

metabolites, the prostamide bimatoprost, which in turn is converted to bimatoprost acid, a prostaglandin F2α receptor agonist, and into 6-(nitrooxy)-hexanoic acid, a NO-donating moiety. As a once-a-day eye drop with a dual mechanism of action, NCX 470 may be able to provide greater IOP lowering compared with primary PGA topical therapy.

NCX 470 exhibited potent and effective IOP-lowering activity in 3 ocular hypertensive animal models.[10] These nonclinical pharmacology studies in well-established animal models of glaucoma and OHT have demonstrated that the IOP-lowering efficacy of NCX 470 is greater than that of equimolar doses of bimatoprost. In particular, the contribution of NO is supported in transient ocular hypertensive rabbits that did not show any IOP lowering in a concurrent masked bimatoprost arm, while NCX 470 lowered IOP, likely via NO release.[10] In addition, an equimolar dose of NCX 470 at 0.042% lowered IOP more effectively than bimatoprost at 0.03% in ocular normotensive dogs, as well as in laser-induced ocular hypertensive non-human primates.[10]

The objectives of the Phase 2 Dolomites trial were to evaluate the safety, tolerability, and IOP-lowering efficacy of NCX 470 at 3 concentrations (0.021%, 0.042% and 0.065%) compared with latanoprost 0.005%, and to determine the optimal concentration of NCX 470 to advance into phase 3 trials.

PATIENTS AND METHODS

The Dolomites trial was a randomized, double-masked, parallel-group, active-control, dose-response trial conducted at 25 clinical sites within the United States (ClinicalTrials.gov ID: NCT03657797). Independent review board (IRB) approval was obtained for each study site before their participation in the trial. The trial was performed in accordance with Good Clinical Practices, the Declaration of Helsinki and subsequent amendments, the US Code of Federal Regulations, and local regulations including the Health Insurance Portability and Accountability Act. Informed consent was obtained from patients before their entry into the trial.

Patients in the Trial

The trial enrolled male and female patients 18 to 85 years old with a diagnosis of bilateral OAG or OHT (OHT must have been documented for at least the past 6 mo) and, if treated, treatment nature and dose regimen must have been stable for both eyes for the 30 days before screening. IOP criteria to be met at 2, postwashout (if applicable) eligibility visits included: IOP $\geq$26 mm Hg at 8:00 AM, $\geq$24 mm Hg at 10:00 AM, and $\geq$22 mm Hg at 4:00 PM in the study eye; IOP $\leq$36 mm Hg in both eyes at all 3 measurement time points; and $\leq$4 mm Hg difference in the mean diurnal IOP values between right and left eyes. To enroll patients responsive to PGAs, those on a PGA or NO-donating PGA therapy at screening were required to have a time-matched IOP increase of $\geq$4 mm Hg in the study eye at both eligibility visits. In addition, patients had to have a best-corrected visual acuity (BCVA) equal to or better than 0.7 logMAR (logarithm of the minimum angle of resolution) (Snellen equivalent ~20/100) in each eye. Female patients must have been incapable of pregnancy or used an effective method of birth control during the study, and those of childbearing potential must have had a negative pregnancy test and not been nursing.

Key exclusion criteria included glaucoma other than OAG; advanced glaucoma; cup/disc ratio $>$0.8; central corneal thickness $<$480 or $>$620 μm; prior placement of a minimally invasive glaucoma device; prior angle surgery or procedures; prior YAG iridotomy or argon laser trabeculoplasty; selective laser trabeculoplasty within the previous 12 months; history of severe dry eye; clinically significant corneal disease or retinal disease; conjunctival hyperemia that was greater than mild; any condition that prevented reliable applanation tonometry; prior corneal laser surgery or refractive keratotomy; and active or recurrent ocular infection or inflammation.

In addition, patients were excluded if they were unwilling or unable to discontinue prestudy IOP-lowering medication(s); had known hypersensitivity or contraindications to PGAs; had anticipated need to initiate or modify medication known to affect IOP; required treatment with corticosteroids; had the uncontrolled systemic disease; and if they were participating in any drug or device clinical investigation within 30 days before screening and/or during the period of study participation.

Treatments and Assessments

After providing written informed consent, potential patients underwent a screening visit examination with included collection of demographic data, a review of ocular and systemic medical history, including concomitant medications, measurement of resting blood pressure and heart rate, collection of blood and urine for clinical laboratory assessments, a urine pregnancy test for women of childbearing potential, refraction and measurement of BCVA, slit-lamp biomicroscopy including assessment of conjunctival hyperemia and iris color, and ophthalmoscopy. IOP was measured in both eyes with a Goldmann applanation tonometer in a masked manner using a 2-person technique. Two consecutive readings were obtained, and if the 2 measurements differed by 2 mm Hg or less, the results were averaged. If they differed by $>$2 mm Hg, a third consecutive reading was taken, and the median IOP recorded. At the screening visit, IOP was measured at 8:00 AM ± 45 minutes, 10:00 AM ± 45 minutes, or 4:00 PM ± 45 minutes. In addition, visual field

testing and gonioscopy were performed if not done within the past 6 months.

Individuals deemed eligible for continuation in the trial had their IOP-lowering medication(s) discontinued at this time, if applicable. However, the initiation of an IOP-lowering medication with a shorter washout period (eg, a topical carbonic anhydrase inhibitor) than the patient's IOP-lowering medication at screening was permitted between the screening and first eligibility visit. The required washout period before the first eligibility visit was 5 days for miotics and oral/topical carbonic anhydrase inhibitors, 14 days for alpha agonists; 28 days for beta-antagonists and all timolol-containing combinations, and 42 days for PGAs, NO-donating PGAs, and rho-kinase inhibitors.

After the appropriate washout period, or after a minimum of 5 days for treatment-naive patients, study visits included 2 eligibility visits held 3 to 7 days apart, visits after 1 week (day 7 ± 2 d), 2 weeks (day 14 ± 2 d), and 4 weeks (day 28—2 d) of therapy, and an exit visit up to 2 days following completion of therapy. Both eligibility visits included a review of any changes in ocular or systemic health, including concomitant medications, measurement of resting blood pressure and heart rate, BCVA, IOP at 8:00 AM ± 30 minutes, 10:00 AM ± 30 minutes, and 4:00 PM ± 30 minutes, and slit-lamp biomicroscopy including assessment of conjunctival hyperemia. In addition, a urine pregnancy test for women of childbearing potential was performed at the first eligibility visit. Pachymetry was performed at the second eligibility visit for all patients.

After confirmation of eligibility, using an Interactive Response Technology (IRT) system, patients were randomized in 1:1:1:1 treatment allocation to 1 of 4 treatment arms: NCX 470 0.021%, NCX 470 0.042%, NCX 470 0.065%, and latanoprost 0.005%. Randomization was also stratified by site and by 8:00 AM baseline IOP in the study eye: average IOP at 8:00 AM of the 2 eligibility visits $\leq$ 28 mm Hg and average IOP at 8:00 AM of the 2 eligibility visits $>$ 28 mm Hg. Treatment assignment was based on a randomization schedule created by a designated unmasked statistician. Each patient was assigned a unique kit with 2 inner boxes, each of which contained one bottle of study medication. Patients were dispensed one box; the remaining box also containing one bottle of study medication, and outer kit remained at the clinical site as a backup in the event the patient lost or inadvertently destroyed their initially dispensed bottle of study medication. For masking purposes, all boxes and bottles were labeled with identical investigational labels. Investigators, study personnel (other than a designee at each site who handled study medication) and patients were masked to the treatments.

Patients were instructed to self-administer or have a caregiver administer study medication to both eyes once daily at 8:00 PM ± 2 hours. Patients also were provided a dosing diary to record compliance to study medication. The dosing diary was collected and reviewed at each subsequent visit.

The week 1, 2, and 4 visits included a review of concomitant medications, measurement of resting blood pressure and heart rate, BCVA, IOP at 8:00 AM ± 30 minutes, 10:00 AM ± 30 minutes, and 4:00 PM ± 30 minutes, and slit-lamp biomicroscopy including assessment of conjunctival hyperemia using a high-resolution color photographic grading scale (grade 0–3 in 0.5 U increments). The week 4 visit also included pachymetry after the last IOP measurement of the day, assessment of iris color, and collection of study medication. The exit visit included a review of concomitant medications, measurement of resting blood pressure and heart rate, BCVA, IOP at 8:00 AM ± 30 minutes, 10:00 AM ± 30 minutes, and 4:00 PM ± 30 minutes, and slit-lamp biomicroscopy including assessment of conjunctival hyperemia. Collection of blood and urine for clinical laboratory assessments, a urine pregnancy test for women of childbearing potential, and dilated ophthalmoscopy were also performed at this visit.

At each visit, patients were encouraged to report adverse events spontaneously or in response to general, nondirected questioning regarding their health.

Endpoints and Statistical Methods

The primary efficacy endpoint was the reduction in mean diurnal IOP from baseline in the study eye (based on the 2 eligibility visits) at week 4. Mean diurnal IOP was defined as the average of the IOP at the 8:00 AM, 10:00 AM, and 4:00 PM time points. Secondary efficacy endpoints included reductions from baseline in time-matched IOP at 8:00 AM, 10:00 AM, and 4:00 PM at week 4 in the study eye, reductions from baseline in mean diurnal IOP measured at the week 1, 2, and exit visits in the study eye and reductions from baseline in time-matched IOP measured at 8:00 AM, 10:00 AM, and 4:00 PM at the week 1, 2, and exit visits in the study eye. The study eye was defined as the eye with the highest baseline mean diurnal IOP value or the right eye if both eyes of a patient had the same IOP value at baseline.

Safety assessments included the incidence and severity of treatment-emergent adverse events (TEAEs), unacceptably high IOP, slit-lamp biomicroscopy parameters, conjunctival hyperemia, dilated ophthalmoscopy, pachymetry, BCVA, vital signs, and clinical laboratory tests. TEAEs were defined as those that developed or worsened following the first dose of study medication and were collected up to the exit visit. Serious adverse events were collected up to 30 days following the last administration of the study medication.

The sample size estimate was based on a noninferiority and superiority test of the difference between NCX 470 and latanoprost with respect to the primary efficacy endpoint. A sample size of 100 completed patients per treatment group provided 99% power to demonstrate noninferiority using a noninferiority limit of −1.5 mm Hg as well as to demonstrate superiority to latanoprost in the reduction from baseline in mean diurnal IOP at week 4 in the study eye for each concentration of NCX 470, assuming a true difference (NCX 470 minus latanoprost) of 2.0 mm Hg, an SD of 3.5 mm Hg at each time point, a correlation of 0.60 among the time points within a patient's study eye, and a 2-sided significance level of 5%. The plan was to randomize a minimum of 420 patients to allow for ~5% discontinuations.

The primary endpoint was evaluated for the intent-to-treat (ITT) population, which comprised all randomized patients, using observed data only and an analysis of covariance (ANCOVA) model with fixed-effect terms for baseline mean diurnal IOP, treatment, and treatment-by-baseline interaction. The treatment-by-baseline interaction term was used to check the appropriateness of the ANCOVA model for testing parallelism among the slopes by treatment group. If the test of parallelism was not significant ($P \geq 0.10$), then the treatment-by-baseline interaction term was dropped from the model, and a reduced ANCOVA model with fixed-effect terms for baseline and treatment was fit. If the test of parallelism was significant

($P < 0.10$), then an analysis of variance model with a fixed-effect term for treatment was performed instead (this model ended up being fit for exit visit analyses only).

Each NCX 470 treatment group was compared with the latanoprost group by computing a 2-sided 95% confidence interval (CI) around the differences between the least squares (LS) mean of each NCX 470 treatment group, and the LS mean of the latanoprost group. The difference was calculated as NCX 470 minus latanoprost. For each comparison, the 2-sided *P*-value was also determined. No adjustments were made for multiple comparisons in this phase 2 study. Noninferiority was determined if the upper limit for the CI around the LS mean difference of NCX 470 minus latanoprost did not exceed 1.5 mm Hg. If noninferiority was determined, superiority was demonstrated if the *P*-value ≤ 0.05 and the upper limit of the 95% CI around the LS mean difference of NCX 470 minus latanoprost did not exceed 0 mm Hg.

Safety analyses were based on the safety population which comprised all randomized patients who received at least 1 dose of study medication. Ocular and nonocular TEAEs were described using discrete summaries at the eye and patient level, respectively, using Medical Dictionary for Regulatory Activities (MedDRA), version 21.0 for coding of the system organ class and preferred term for each treatment group. TEAEs were also classified by severity and relationship to study medication. Vital signs, clinical laboratory tests, IOP, slit-lamp biomicroscopy (including anterior chamber cells and anterior chamber flare), conjunctival hyperemia, dilated ophthalmoscopy, pachymetry, and BCVA were summarized using discrete or continuous summary statistics, as appropriate.

RESULTS

Patient Disposition

Patients were enrolled from August 2018 to August 2019. Of the 656 patients who were screened, 433 were randomized to treatment with NCX 470 0.021% (n = 111), NCX 470 0.042% (n = 108), NCX 470 0.065% (n = 107), or latanoprost 0.005% (n = 107). The primary reason for screen failures was IOP that did not meet inclusion criteria. All randomized patients received at least 1 dose of study medication and were included in the safety population and in the ITT population (N = 433). The per-protocol population included 415 patients (n = 108 NCX 470 0.021%; n = 106 NCX 470 0.042%; n = 100 NCX 470 0.065%; and n = 101 latanoprost). Reasons for excluding patients from the per-protocol population included inadequate washout from prior IOP-lowering medications (n = 1), use of prohibited concomitant medications (n = 2), missed or out of protocol-specified window for week 2 or 4 visits (n = 7) and missed or out of protocol-specified window for dosing study medication the evening before the week 2 or 4 visits (n = 8). The discontinuation rate was very low; overall, 98% (425) patients completed the study and only 2% (8) discontinued from study (n = 3 NCX 470 0.042%; n = 5 NCX 470 0.065%). Reasons for discontinuation included adverse event (n = 2 NCX 470 0.065%), lost to follow up (n = 1 NCX 470 0.042%; n = 1 NCX 470 0.065%), investigator decision (n = 1 NCX 470 0.042%) and withdrawal by patient (n = 1 NCX 470 0.042%; n = 2 NCX 470 0.065%).

Patient Demographics and Baseline Characteristics

The ITT population comprised 433 patients ranging in age from 18 to 84 years old, of whom 240 (55%) were female, 287 (66%) were white, and 356 (82%) identified as being not of Hispanic or Latino ethnicity (Table 1). Demographics and study eye baseline characteristics, including mean diurnal IOP, central corneal thickness and BCVA, were generally comparable between treatment groups. However, there was a trend towards an imbalance in sex distribution between treatment groups ($P = 0.0710$) with the NCX 470 0.042% group having a higher percentage of females (65.7%) than the other treatment groups (maximum 54.2%). The majority of patients in all groups had used a PGA in the 12 months before screening, with latanoprost being the mostly commonly reported medication.

Efficacy

All treatments resulted in significant reductions from baseline in the study eye mean diurnal IOP at week 1, 2, and 4 visits (1-sample *t* test; $P < 0.0001$).

Among NCX 470 groups, LS mean diurnal IOP changes from baseline to week 4 were dose-dependent in a linear manner without plateau or attenuation of increased IOP lowering with each increasing concentration (−7.83, −8.24, and −8.67 mm Hg, respectively). In comparison, the IOP change from baseline for latanoprost was −7.43 mm Hg, resulting in LS mean differences (NCX 470 minus latanoprost) of −0.40, −0.81, and −1.23 mm Hg for 0.021%, 0.042%, and 0.065%, respectively (Table 2). Noninferiority of the 0.021%, 0.042%, and 0.065% concentrations of NCX 470 to latanoprost in the ITT population was demonstrated based on the upper limit of the 95% CI around the LS mean difference of NCX 470 minus latanoprost being <1.5 mm Hg.

The superiority of the 0.042% and 0.065% concentrations of NCX 470 to latanoprost for mean diurnal IOP reduction from baseline at week 4 was demonstrated based on the upper limit of the 95% CI for the LS mean differences of <0, and with *P*-values of 0.0281 and 0.0009, respectively (Table 2; Fig. 2).

In addition, at the week 1, 2, and exit visits all 3 concentrations of NCX 470 were noninferior to latanoprost based on the difference in the treatment effect between each NCX 470 dose and latanoprost 0.005% for change from baseline in mean diurnal IOP (Table 2). The 0.065% dose of NCX 470 demonstrated a significantly greater change from baseline compared with latanoprost ($P = 0.0040$, 0.0174, and 0.0093, respectively).

Evaluations of mean IOP changes from baseline at the 8:00 AM, 10:00 AM, and 4:00 PM diurnal time points at the week 1, 2, 4, and exit visits showed that all doses of NCX 470 were noninferior to latanoprost for IOP-lowering efficacy based on analyses of mean change from baseline in time-matched IOP. Moreover, changes from baseline in mean IOP were significantly greater than those in the latanoprost group for the NCX 470 0.065% group at 10:00 AM and 4:00 PM ($P = 0.0044$ and 0.0013, respectively) at week 1, at 8:00 AM and 4:00 PM ($P = 0.0166$ and 0.0291, respectively) at week 2, at 8:00 AM, 10:00 AM, and 4:00 PM ($P = 0.0214$, 0.0008, and 0.0015, respectively) at week 4 (Fig. 3); and at 8:00 and 10:00 AM ($P = 0.0037$ and 0.0354, respectively) at the exit visit, as well as for the NCX 470 0.042% group at 4:00 PM at the week 1 and 4 visits ($P = 0.0262$ and 0.0022, respectively).

Safety

The median number of days of exposure to study medication was 27.0 days for all treatment groups.

TABLE 1. Patient Demographics and Study Eye Baseline Characteristics (Intent-to-treat population)

	n (%)				
	NCX 470 0.021% (N = 111)	NCX 470 0.042% (N = 108)	NCX 470 0.065 % (N = 107)	Latanoprost 0.005% (N = 107)	*P*
Age (y)					0.3648*
Mean (SD)	63.8 (12.4)	65.6 (9.0)	63.4 (11.0)	63.2 (11.8)	
Minimum, maximum	24, 83	33, 82	18, 83	25, 84	
Age category (y)					0.4668†
≥ 18 to <65	48 (43.2)	46 (42.6)	53 (49.5)	55 (51.4)	
≥ 65	63 (56.8)	62 (57.4)	54 (50.5)	52 (48.6)	
Sex					0.0710†
Male	57 (51.4)	37 (34.3)	49 (45.8)	50 (46.7)	
Female	54 (48.6)	71 (65.7)	58 (54.2)	57 (53.3)	
Race					0.9570†
American Indian or Alaska Native	0	0	1 (0.9)	0	
Asian	2 (1.8)	1 (0.9)	3 (2.8)	1 (0.9)	
Black or African American	35 (31.5)	32 (29.6)	32 (29.9)	35 (32.7)	
White	72 (64.9)	74 (68.5)	71 (66.4)	70 (65.4)	
Multiracial	2 (1.8)	1 (0.9)	0	1 (0.9)	
Ethnicity					0.7238†
Hispanic or Latino	23 (20.7)	20 (18.5)	16 (15.0)	18 (16.8)	
Not Hispanic or Latino	88 (79.3)	88 (81.5)	91 (85.0)	89 (83.2)	
Baseline mean diurnal IOP (mm Hg)					0.7157*
Mean (SD)	26.62 (1.66)	26.89 (1.99)	26.80 (2.07)	26.68 (1.75)	
Median	26.25	26.21	26.17	26.33	
Minimum, maximum	24.0, 31.5	24.1, 32.3	24.1, 34.3	24.1, 33.8	
Central corneal thickness (μm)					0.3905*
Mean (SD)	552.9 (33.9)	559.7 (32.4)	553.9 (30.5)	555.0 (29.2)	
Median	553.0	564.0	554.0	553.0	
Minimum, maximum	488, 620	481, 618	484, 616	488, 618	
Best-corrected visual acuity (logMAR)					0.2498*
Mean (SD)	0.037 (0.108)	0.054 (0.120)	0.056 (0.127)	0.029 (0.106)	

**P*-values based on Analysis of Variance.
†*P*-values based on Freeman-Halton test.
IOP indicates intraocular pressure; logMAR, logarithm of the minimum angle of resolution.

Compliance with study medication dosing ranged from 96% to 100% among treatment groups.

A greater proportion of patients in the NCX 470 0.021%, 0.042% and 0.065% treatment groups [34 (30.6%) of 111, 52 (48.1%) of 108, and 50 (46.7%) of 107, respectively] experienced at least 1 ocular TEAE compared with those in the latanoprost group [21 (19.6%) of 107] (Table 3).

The most commonly reported TEAE in all treatment groups was conjunctival hyperemia which was experienced by 12 (10.8%) of 111, 24 (22.2%) of 108, and 18 (16.8%) of 107 patients in the NCX 470 0.021%, 0.042%, and 0.065% groups, respectively, and 7 (6.5%) of 107 patients in the latanoprost group (Table 3). All TEAEs of conjunctival hyperemia in the NCX 470 treatment groups were considered to be related to study drug and were mild (85%) or moderate (15%); none were severe. Withdrawal due to conjunctival hyperemia was infrequent, leading to only 1 patient in each of the NCX 470 0.042% and 0.065% groups to withdraw from the study.

The second most commonly reported TEAE in all treatment groups was instillation site pain (ie, ocular burning or stinging upon instillation) reported by 8 (7.2%) of 111, 10 (9.3%) of 108, and 12 (11.2%) of 107 patients in the NCX 470 0.021%, 0.042%, and 0.065% groups, respectively, and 6 (5.6%) of 107 patients in the latanoprost group. All TEAEs of instillation site pain were considered to be related to study drug and were of mild severity.

The only serious ocular TEAE in the trial occurred in a patient who received NCX 470 0.042% and experienced endophthalmitis following cataract surgery, 23 days after the patient had completed the study.

Three patients reported a total of 4 ocular TEAEs leading to withdrawal of the study drug. These included conjunctival hyperemia and dry eye reported by a single patient in the NCX 470 0.042% group, and instillation site pain and conjunctival hyperemia each reported by single patients in the NCX 470 0.065% group.

The most commonly reported nonocular TEAE was upper respiratory tract infection, reported in a maximum of 3 (2.8%) of 107 patients in any treatment group. All nonocular TEAEs were considered unrelated to study drug.

Three nonocular serious TEAEs, all considered unrelated to the study drug, were reported: transient ischemic attack, hypertension, and B-cell lymphoma reported by 1 patient each in the NCX 470 0.021%, 0.042%, and 0.065% groups, respectively. The latter TEAE led to withdrawal from the study.

In addition to evaluating the frequency and severity of patient-reported TEAEs for conjunctival hyperemia at week 1, 2, and 4 visits, conjunctival hyperemia was graded by the investigator using a high-resolution color photographic grading scale. Mean conjunctival hyperemia scores in the

TABLE 2. IOP (mm Hg) Change From Baseline at the Week 1, 2, 4, and Exit Visits

IOP Change From Baseline	NCX 470 0.021% (N = 111)	NCX 470 0.042% (N = 108)	NCX 470 0.065% (N = 107)	Latanoprost 0.005% (N = 107)
Week 1				
Mean diurnal				
LS mean	−7.78	−8.09	−8.64	−7.56
LS mean difference	−0.22	−0.53	−1.08	
95% CI for LS mean difference	−0.94, 0.51	−1.25, 0.20	−1.82, −0.35	
P (vs. latanoprost)	0.5560	0.1556	0.0040	
8:00 AM				
LS mean	−8.56	−8.77	−9.25	−8.52
LS mean difference	−0.04	−0.26	−0.74	
95% CI for LS mean difference	−0.87, 0.78	−1.09, 0.57	−1.57, 0.10	
P (vs. latanoprost)	0.9204	0.5426	0.0824	
10:00 AM				
LS mean	−7.86	−8.09	−8.93	−7.70
LS mean difference	−0.16	−0.38	−1.22	
95% CI for LS mean difference	−0.99, 0.67	−1.21, 0.45	−2.06, −0.38	
P (vs. latanoprost)	0.7043	0.3646	0.0044	
4:00 PM				
LS mean	−6.94	−7.37	−7.78	−6.48
LS mean difference	−0.46	−0.89	−1.30	
95% CI for LS mean difference	−1.23, 0.32	−1.67, −0.11	−2.08, −0.51	
P (vs. latanoprost)	0.2471	0.0262	0.0013	
Week 2				
Mean diurnal				
LS mean	−8.01	−8.32	−8.84	−8.02
LS mean difference	0.01	−0.30	−0.82	
95% CI for LS mean difference	−0.66, 0.68	−0.97, 0.38	−1.50, −0.15	
P (vs. latanoprost)	0.9788	0.3863	0.0174	
8:00 AM				
LS mean	−8.83	−8.76	−9.79	−8.80
LS mean difference	−0.02	0.04	−0.99	
95% CI for LS mean difference	−0.82, 0.77	−0.76, 0.85	−1.80, −0.18	
P (vs. latanoprost)	0.9537	0.9193	0.0166	
10:00 AM				
LS mean	−8.15	−8.49	−8.96	−8.30
LS mean difference	0.15	−0.20	−0.67	
95% CI for LS mean difference	−0.61, 0.90	−0.96, 0.57	−1.43, 0.10	
P (vs. latanoprost)	0.7006	0.6150	0.0884	
4:00 PM				
LS mean	−7.11	−7.63	−7.79	−6.98
LS mean difference	−0.13	−0.65	−0.81	
95% CI for LS mean difference	−0.84, 0.59	−1.37, 0.08	−1.53, −0.08	
P (vs. latanoprost)	0.7287	0.0800	0.0291	
Week 4				
Mean diurnal				
LS mean	−7.83	−8.24	−8.67	−7.43
LS mean difference	−0.40	−0.81	−1.23	
95% CI for LS mean difference	−1.11, 0.31	−1.52, −0.09	−1.96, −0.51	
P (vs. latanoprost)	0.2666	0.0281	0.0009	
8:00 AM				
LS mean	−8.74	−8.88	−9.45	−8.46
LS mean difference	−0.28	−0.41	−0.98	
95% CI for LS mean difference	−1.10, 0.55	−1.24, 0.42	−1.82, −0.15	
P (vs. latanoprost)	0.5100	0.3305	0.0214	
10:00 AM				
LS mean	−7.96	−8.20	−8.94	−7.53
LS mean difference	−0.43	−0.67	−1.41	
95% CI for LS mean difference	−1.24, 0.37	−1.49, 0.15	−2.23, −0.59	
P (vs. latanoprost)	0.2912	0.1072	0.0008	
4:00 PM				
LS mean	−6.83	−7.55	−7.60	−6.32
LS mean difference	−0.51	−1.23	−1.28	
95% CI for LS mean difference	−1.28, 0.26	−2.01, −0.45	−2.06, −0.49	
P (vs. latanoprost)	0.1934	0.0022	0.0015	
Exit				
Mean diurnal				
LS mean	−4.95	−5.59	−5.98	−4.89
LS mean difference	−0.06	−0.71	−1.10	

TABLE 2. (*continued*)

IOP Change From Baseline	NCX 470 0.021% (N = 111)	NCX 470 0.042% (N = 108)	NCX 470 0.065% (N = 107)	Latanoprost 0.005% (N = 107)
95% CI for LS mean difference	−0.87, 0.75	−1.53, 0.11	−1.92, −0.27	
P (vs. latanoprost)	0.8796	0.0912	0.0093	
8:00 AM				
LS mean	−5.66	−5.91	−6.92	−5.49
LS mean difference	−0.17	−0.43	−1.44	
95% CI for LS mean difference	−1.12, 0.78	−1.39, 0.53	−2.40, −0.47	
P (vs. latanoprost)	0.7208	0.3843	0.0037	
10:00 AM				
LS mean	−5.10	−5.74	−6.02	−5.02
LS mean difference	−0.09	−0.72	−1.00	
95% CI for LS mean difference	−1.00, 0.83	−1.65, 0.21	−1.94, −0.07	
P (vs. latanoprost)	0.8514	0.1268	0.0354	
4:00 PM				
LS mean	−4.16	−4.99	−5.01	−4.19
LS mean difference	0.03	−0.80	−0.83	
95% CI for LS mean difference	−0.89, 0.95	−1.73, 0.13	−1.76, 0.11	
P (vs. latanoprost)	0.9500	0.0908	0.0837	

LS mean difference calculated as NCX 470 minus latanoprost.
Baseline refers to the average of the IOP values at the 2 eligibility visits.
CI indicates confidence interval; IOP, intraocular pressure; LS, least squares.

NCX 470 treatment groups were numerically higher than in the latanoprost group and were highest with the 0.042% dose at all visits. At the week 4 visit, the mean (SD) scores in the study eyes of the NCX 470 0.021%, 0.042%, and 0.065% groups were 0.64 (0.60), 0.69 (0.53), and 0.66 (0.59), respectively, and in the study eyes of latanoprost group was 0.49 (0.51). Furthermore, for study and fellow eyes in all NCX 470 treatment groups, mean change from baseline was <0.50 score units (on a scale ranging from 0 to 3 in 0.5 U increments) at all visits, and few NCX 470-treated eyes had scores of >2 at any visit.

There were no safety concerns based on an analysis of clinical laboratory parameters (hematology, blood chemistries, urinalysis), vital signs (systolic and diastolic blood pressure, pulse rate), BCVA, slit-lamp biomicroscopy parameters (eyelid, conjunctiva, cornea, lens, iris/pupil, and anterior chamber), anterior chamber cells or flare, iris color, pachymetry, unacceptably high IOP, and dilated ophthalmoscopy parameters (vitreous, retina, macula, choroid, and optic nerve including horizontal and vertical cup-to-disc ratio).

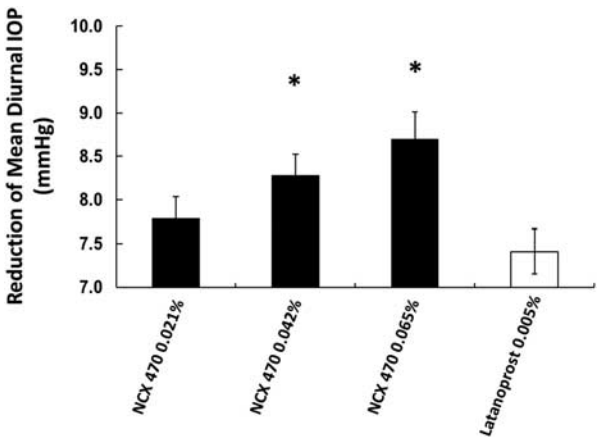

FIGURE 2. Reduction from baseline in mean diurnal intraocular pressure (IOP) at week 4 for NCX 470 (0.021%, 0.042%, and 0.065%) and latanoprost (±SE; intent-to-treat population). *Statistically significantly greater IOP reductions compared with latanoprost ($P < 0.05$).

DISCUSSION

In this study, NCX 470 demonstrated clinically relevant and statistically significant IOP reductions over the 4-week study period at all tested doses of NCX 470, with maximal efficacy observed with NCX 470 0.065%. The dose-dependent increase in IOP-lowering efficacy of NCX 470 was linear suggesting that additional IOP reduction with concentrations above the highest tested NCX 470 0.065% may be possible. The clinical dose ranging in this study included a low dose of 0.021% NCX 470 (equimolar to 0.015% bimatoprost), a mid-dose of 0.042% NCX 470 (equimolar with 0.03% bimatoprost), and a high dose of 0.065% NCX 470 (equimolar to 0.05% bimatoprost).

Bimatoprost and NO provide robust IOP-lowering activity by concomitantly activating 2 independent mechanisms: secondary uveoscleral outflow via bimatoprost and primary trabecular/Schlemm canal conventional outflow via NO.[11,12] NO donors lower IOP by relaxing the trabecular meshwork and increasing aqueous humor outflow.[12–14]

The nature of the IOP-lowering treatment effect due to NCX 470, which demonstrated statistically significant superiority of the 0.042% and 0.065% concentrations versus latanoprost 0.005%, is more likely due to the NO-donating mechanism of action of NCX 470 rather than due to the additional amount of bimatoprost beyond the 0.03% threshold delivered by NCX 470 0.042%.

Over the last 2 decades, PGAs have unequivocally become the first-line pharmacotherapy for reduction of IOP, yet timolol has been the most commonly selected active comparator in clinical studies of IOP-lowering agents. In consideration of this reality, latanoprost was chosen as a more relevant head-to head comparator in this study.

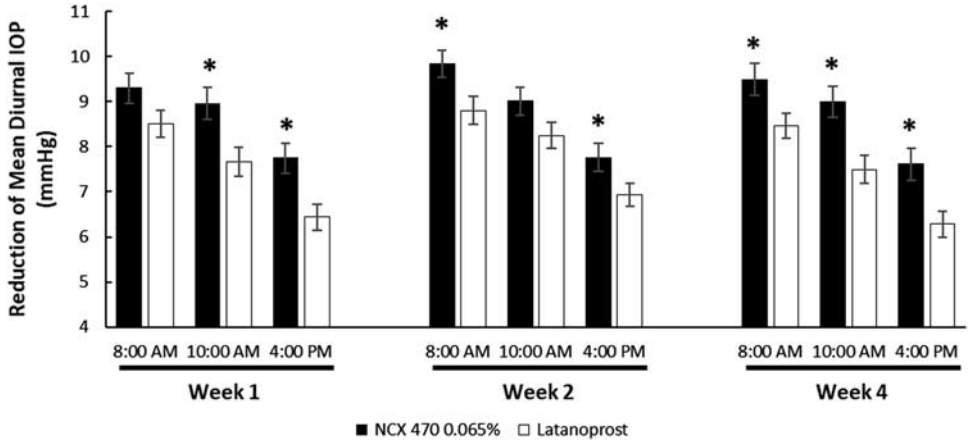

FIGURE 3. Mean intraocular pressure (IOP) reduction from baseline for NCX 470 0.065% and latanoprost at 8:00 AM, 10:00 AM, and 4:00 PM at weeks 1, 2, and 4 (± SE; intent-to-treat population). *Statistically significantly greater IOP reduction compared with latanoprost ($P < 0.05$).

As NCX 470 contains bimatoprost covalently linked to an NO-donating group, it remains of interest in the future to compare an equimolar amount of bimatoprost (eg, bimatoprost ophthalmic solution 0.03%) with the equimolar NCX 470 delivered bimatoprost (eg, NCX 470 ophthalmic solution 0.042%) to demonstrate the additional IOP-lowering effect via NO. Such experiments have been completed in vivo in 2 species, demonstrating that the additional

TABLE 3. TEAEs

	n (%)			
	NCX 470 0.021% (N = 111)	**NCX 470 0.042% (N = 108)**	**NCX 470 0.065% (N = 107)**	**Latanoprost 0.005% (N = 107)**
Summary of events				
Any ocular TEAE	34 (30.6)	52 (48.1)	50 (46.7)	21 (19.6)
Any nonocular TEAE	11 (9.9)	9 (8.3)	11 (10.3)	10 (9.3)
Any serious ocular TEAE	0	1 (0.9)	0	0
Any serious nonocular TEAE	1 (0.9)	1 (0.9)	1 (0.9)	0
Any serious ocular TEAE related to study medication	0	0	0	0
Any serious nonocular TEAE related to study medication	0	0	0	0
AEs reported in ≥2 patients in any treatment group, by MedDRA SOC and PT				
Eye disorders				
Conjunctival hyperemia	12 (10.8)	24 (22.2)	18 (16.8)	7 (6.5)
Ocular hyperemia	5 (4.5)	9 (8.3)	10 (9.3)	5 (4.7)
Eye pruritus	2 (1.8)	1 (0.9)	6 (5.6)	0
Eye irritation	1 (0.9)	2 (1.9)	3 (2.8)	1 (0.9)
Punctate keratitis	3 (2.7)	2 (1.9)	1 (0.9)	0
Conjunctival hemorrhage	1 (0.9)	1 (0.9)	2 (1.9)	0
Lacrimation increased	2 (1.8)	1 (0.9)	1 (0.9)	1 (0.9)
Dry eye	0	2 (1.9)	1 (0.9)	0
Vision blurred	0	0	3 (2.8)	0
Eye discharge	2 (1.8)	0	0	0
Eye pain	1 (0.9)	0	0	2 (1.9)
General disorders and administration site conditions				
Instillation site pain	8 (7.2)	10 (9.3)	12 (11.2)	6 (5.6)
Instillation site pruritus	2 (1.8)	5 (4.6)	3 (2.8)	3 (2.8)
Instillation site discomfort	2 (1.8)	1 (0.9)	0	0
Instillation site dryness	0	2 (1.9)	0	0
Infections and infestations				
Upper respiratory tract infection	2 (1.8)	2 (1.9)	3 (2.8)	3 (2.8)
Nasopharyngitis	0	1 (0.9)	1 (0.9)	2 (1.9)
Investigations				
Vital dye staining cornea present	1 (0.9)	1 (0.9)	3 (2.8)	1 (0.9)

AE indicates adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.

IOP lowering comes from the NO-donating group of NCX 470,[10] but to date, such comparisons have not been performed in clinical trials.

Reductions in mean diurnal IOP at week 4—the primary efficacy endpoint in this study—for all 3 concentrations of NCX 470 (0.021%, 0.042% and 0.065%) were noninferior to those produced by latanoprost 0.005%, and were statistically significantly greater with NCX 470 0.042% and NCX 470 0.065% compared with latanoprost. Reductions in mean diurnal IOP at the week 1, 2, and exit visits for all 3 concentrations of NCX 470 also were noninferior to latanoprost, and significantly greater with NCX 0.065% versus latanoprost at all 3 visits.

The IOP reductions at the 8:00 AM, 10:00 AM, and 4:00 PM time points at week 1, 2, and 4 visits ranged from 7.60 to 9.79 mm Hg with NCX 470 0.065% compared with 6.32 to 8.80 mm Hg with latanoprost 0.005%. The difference in time-matched IOP reduction was up to 1.41 mm Hg greater with NCX 470 0.065% compared with latanoprost. The clinical significance of the greater IOP reduction with NCX 470 0.065% relative to latanoprost 0.005% is highlighted by the results of the Early Manifest Glaucoma Trial which found that for each mm Hg of IOP reduction from baseline in the first 3 months of treatment there was an ~10% reduction in visual field loss.[3] More recently, based on the results of the UK Glaucoma Treatment study which evaluated the time to visual field progression in patients with newly diagnosed OAG randomized to latanoprost 0.005% versus placebo,[15] Heijl[16] concluded that the reduction in risk of visual field progression was ~19% for each mm Hg of IOP reduction and noted that this finding makes the case for the continued development of new and even more potent IOP-lowering agents.

The assessment of safety demonstrated that once-daily dosing with NCX 470 0.021%, 0.042% or 0.065% for 4 weeks was well tolerated. Conjunctival hyperemia was the most commonly reported event and was mostly mild or moderate in severity; hyperemia led to study withdrawal only of single patients in each of the NCX 470 0.042% and 0.065% treatment groups.

The limitation of the trial was its short duration which did not allow for evaluation of TEAEs such as increased pigmentation of the iris and periorbital tissues, changes to eyelashes, and deepening of the upper eyelid sulcus which are more likely to be observed with long term dosing of PGAs. However, trials of 4-week duration are common to evaluate dose-response of topical IOP-lowering medications.[17,18] Phase 3 clinical trials will evaluate the safety and efficacy of NCX 470 for up to 12 months. In addition, given that NCX 470 is a NO-donating bimatoprost, bimatoprost may have been an interesting comparator. However, latanoprost was considered as the most relevant comparator given its wide use in clinical practice, and its well-established safety and efficacy profile.[19]

In conclusion, NCX 470 was noninferior to latanoprost and generally well tolerated at all doses studied. The dose-dependent response suggests that concentrations higher than 0.065% may provide even greater IOP-lowering efficacy in future clinical trials. Therefore, NCX 470 0.065% and a higher concentration, NCX 470 0.1%, have been selected for further clinical evaluation in comparison with latanoprost 0.005%.

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REFERENCES

1. Jonas JB, Aung T, Bourne RR, et al. Glaucoma. *Lancet*. 2017; 309:2183–2193.
2. Tham YC, Li X, Wong TY, et al. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. *Ophthalmology*. 2014;121: 2081–2090.
3. Leske MC, Heijl A, Hussein M, et al. Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. *Arch Ophthalmol*. 2003;121:48–56.
4. Daka Q, Trkulja V. Efficacy and tolerability of mono-compound topical treatments for reduction of intraocular pressure in patients with primary open angle glaucoma or ocular hypertension: an overview of reviews. *Croat Med J*. 2014;55:468–480.
5. Noecker RS, Dirks MS, Choplin NT, et al. A six-month randomized clinical trial comparing the intraocular pressure lowering efficacy of bimatoprost and latanoprost in patients with ocular hypertension or glaucoma. *Am J Ophthalmol*. 2003;135:55–63.
6. Parrish RK, Palmberg P, Sheu WP, et al. A comparison of latanoprost, bimatoprost, and travoprost in patients with elevated intraocular pressure: a 12-week, randomized, masked-evaluator multicenter study. *Am J Ophthalmol*. 2003;135: 688–703.
7. Gandolfi S, Simmons ST, Sturm R, et al. Bimatoprost Study Group 3. Three-month comparison of bimatoprost and latanoprost in patients with glaucoma and ocular hypertension. *Adv Ther*. 2001;18:110–121.
8. Medeiros FA, Martin KR, Peace J, et al. Comparison of latanoprostene bunod 0.024% and timolol maleate 0.5% in open-angle glaucoma or ocular hypertension: the LUNAR Study. *Am J Ophthalmol*. 2016;168:250–259.
9. Weinreb RN, Sforzolini BS, Vittitow J, et al. Latanoprostene bunod 0.024% versus timolol maleate 0.5% in subjects with open-angle glaucoma or ocular hypertension: the APOLLO study. *Ophthalmology*. 2016;123:965–973.
10. Impagnatiello F, Toris CB, Batugo M, et al. Intraocular pressure-lowering activity of NCX 470, a novel nitric oxide-donating bimatoprost in preclinical models. *Invest Ophthalmol Vis Sci*. 2015;56:6558–6564.
11. Woodward DF, Krauss AHP, Nilsson SFE. Bimatoprost effects on aqueous humor dynamics in monkeys. *J Ophthalmol*. 2010;2010:926192.
12. Cavet ME, Vittitow JL, Impagnatiello F, et al. Nitric oxide (NO): an emerging target for the treatment of glaucoma. *Invest Ophthalmol Vis Sci*. 2014;55:5005–5015.

13. Gabelt BT, Kaufman PL, Rasmussen CA. Effect of nitric oxide compounds on monkey ciliary muscle in vitro. *Exp Eye Res*. 2011;93:321–327.
14. Heyne GW, Kiland JA, Kaufman PL, et al. Effect of nitric oxide on anterior segment physiology in monkeys. *Invest Ophthalmol Vis Sci*. 2013;54:5103–5110.
15. Garway-Heath DF, Crabb DP, Bunce C, et al. Latanoprost for open-angle glaucoma (UKGTS): a randomised, multicentre, placebo-controlled trial. *Lancet*. 2014;385:1295–1304.
16. Heijl A. Glaucoma treatment: by the highest level of evidence. *Lancet*. 2015;385:1264–1266.
17. Weinreb RN, Ong T, Sforzolini BS, et al. A randomised, controlled comparison of latanoprostene bunod and latanoprost 0.005% in the treatment of ocular hypertension and open angle glaucoma: the VOYAGER Study. *Br J Ophthalmol*. 2015;99:738–745.
18. Bacharach J, Dubiner HB, Levy B, et al. Double-masked, randomized, dose-response study of AR-13324 versus latanoprost in patients with elevated intraocular pressure. *Ophthalmology*. 2015;122:302–307.
19. Alm A. Latanoprost in the treatment of glaucoma. *Clin Ophthalmol*. 2014;8:1967–1985.

