The predominant risk factor for the progression of glaucoma is an elevated IOP due to reduced aqueous humor (AH) outflow facility through the trabecular meshwork and Schlemm’s canal outflow pathway (i.e., conventional pathway).\(^1\) The trabecular outflow pathway drains 60% to 90% of the AH under physiologic conditions while the remainder of AH exits via the uveoscleral drainage pathway, with its relative contribution increasing in conditions of sustained IOP elevation.\(^1,2\)

Prostaglandin F2alpha (PGF2\(\alpha\)) analogues are the most widely prescribed IOP-lowering drugs, mainly acting by increasing uveoscleral outflow.\(^3\) They include latanoprost, travoprost, tafluprost, and bimatoprost, with the latter being the least potent in vivo but among the most effective of the PGF2\(\alpha\) analogues.\(^4\) However, more than other PGF2\(\alpha\) analogues, bimatoprost can cause eye redness and changes to eye pigmentation and eyelash length at clinically effective doses.\(^5\)

Converging evidence indicates that nitric oxide (NO) via soluble guanylyl cyclase activation and cGMP formation in target ocular tissues (where it serves as a surrogate marker for NO release) regulates AH formation\(^6\) and drainage via conventional outflow,\(^7\) thereby lowering IOP.\(^8,9\) Accordingly, a variety of NO donors have been shown to lower IOP in multiple experimental conditions and in glaucomatous patients. For example, topical administration of the NO donors glyceryl trinitrate (GTN), isosorbide dinitrate, sodium nitrite, and sodium nitroprusside (SNP) rapidly lowered IOP with a peak effect at 1 or 2 hours in a normotensive rabbit model.\(^10\) With few exceptions,\(^11\) in nonhuman primates, the topical administration of NO donors, that is, GTN, at doses as low as 0.1% significantly decreased IOP in ocular normotensive conditions.\(^12\) In addition, the NO donor SNP enhanced the efficacy of latanoprost,\(^13\) suggesting a synergistic effect of PGF2\(\alpha\) and NO in lowering IOP likely because of the complementary cellular and molecular mechanisms of PGF2\(\alpha\) and NO that...
affect uveoscleral and trabecular outflow pathways, respectively.

More importantly, this latter concept has been confirmed recently in glaucoma and ocular hypertensive patients with Ves neo (latanoprostene bunod), a dual-acting NO-donating latanoprost currently in clinical development for the treatment of glaucoma and ocular hypertension.14,15 In addition to the IOP-lowering activity, NO delivery to the eye is largely safe and well tolerated in most species including humans14 even at high concentrations,16 making it an ideal candidate to widen the therapeutic index of bimatoprost.

**Materials and Methods**

In all experiments, animals were cared for and treated in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. Experiments were performed in accordance with protocols approved by the Animal Care Committees of the sites, and all efforts were made to limit the number of animals and to minimize animal discomfort.

**Drugs and Treatments**

NCX 470 was synthesized in a three-step synthesis starting from bimatoprost. Briefly, bimatoprost was reacted with butylboronic acid and then with 6-bromohexanoyl chloride to obtain intermediate 1 [(E)-1-(1R,2R,3S,4S)-5-[(2Z)-6-(ethylcarbamoyl)hex-2-ene-1-yl]-2,4-dioxo-3-horabicyclo[3.2.1]octan-6-yl]-5-phenylpent-1-en-3-yl 6-nitrooxy]hexanoate] is a novel NO-donating bimatoprost with potentially greater IOP-lowering efficacy than bimatoprost, which would allow the use of low and safe doses while retaining IOP-lowering activity similar to or superior to bimatoprost itself. The purpose of this study was to test this hypothesis in a head-to-head comparison of NCX 470 and bimatoprost at equimolar doses in three well-established animal models of glaucoma. Specifically, transiently ocular hypertensive New Zealand white rabbits (tOHT-Rabbits) previously shown to respond to NO17 and not as much to PGF2α agonists13,18 were chosen to dissect the NO contribution from that of bimatoprost. Ocular normotensive dogs (ONT-Dogs) and hypertensive nonhuman primates (OHT- Monkeys) were instead selected as species sensitive to both PGF2α analogues and NO.18 Finally, we also monitored the concentrations of NCX 470 or bimatoprost, bimatoprost acid, and cGMP in ocular tissues following topical dosing with NCX 470 or bimatoprost in naïve pigmented Dutch Belted rabbits to ascertain potential differences in the absorption profile of the two compounds.

**IOP Measurements**

Transiently Ocular Hypertensive New Zealand White Rabbits (tOHT-Rabbits). A previously described method was generally followed.13 Briefly, male New Zealand white rabbits weighing 2.0 to 2.5 kg were anaesthetized using 20 mg/mL/kg sodium pentobarbital and injected with 0.1 mL hypertonic saline solution (5% in distilled water) into the vitreous of both eyes. Intraocular pressure (IOP) was determined using a pneumotonometer (Model 30; Reichert, Depew, NY, USA) prior to hypertonic saline injection (baseline) and at 0.5, 1, 1.5, 3, and 5 hours thereafter. Vehicle or drugs were instilled immediately after the injection of hypertonic saline. Eyes were randomly assigned to different treatment groups. Vehicle (n = 17) and drugs (n = 7 for NCX 470 0.1% and n = 7 for bimatoprost 0.1%) were directly instilled into the conjunctiva.
TABLE 1. Bimatoprost-Free Acid in Ocular Tissues Following Topical NCX 470 (30 μL, 0.042%) and Bimatoprost (30 μL, 0.03%) Dosing in Dutch Belted Rabbits

<table>
<thead>
<tr>
<th>Compound</th>
<th>Tissue</th>
<th>T\text{max}, h</th>
<th>C\text{max}, ng/mL or g Tissue</th>
<th>AUC\text{0-18}, ng*h/mL or g Tissue</th>
<th>t\text{1/2}, h</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCX 470</td>
<td>AH</td>
<td>1.0</td>
<td>139 ± 37</td>
<td>534 ± 50*</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>CR</td>
<td>1.0</td>
<td>555 ± 204</td>
<td>1099 ± 210</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>ICB</td>
<td>1.0</td>
<td>60.2 ± 15.1</td>
<td>207 ± 20</td>
<td>1.7</td>
</tr>
<tr>
<td>Bimatoprost</td>
<td>AH</td>
<td>1.0</td>
<td>54.4 ± 15.7</td>
<td>182 ± 28</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>CR</td>
<td>1.0</td>
<td>248 ± 87</td>
<td>682 ± 113</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>ICB</td>
<td>4.0</td>
<td>20.2 ± 2.4</td>
<td>157 ± 18</td>
<td>5.0</td>
</tr>
</tbody>
</table>

Data are reported as mean ± SEM (calculated in WinNonlin using sparse sampling module).

* P < 0.05 versus respective value in bimatoprost-treated eyes.

pocket at desired doses. One topical drop of proparacaine HCl 0.13% was applied to the eye prior to IOP readings.

**Ocular Normotensive Dogs (ONT-Dogs).** Ocular normotensive beagle dogs were used. Intraocular pressure measurements were recorded with a pneumotonometer (Model 30; Reichert, Depew, NY, USA), and animal dosing was performed either in the morning (AM) or in the evening (PM) to monitor potential differences in the resulting diurnal IOP following these two different treatment paradigms. The drug eye for each dog was selected at random, and all measurements were taken by an experienced investigator blind to the treatment at 0 (baseline), 2, 4, 6, and 24 hours post AM dosing or at 0 (baseline), 12, and 18 hours post PM dosing in a separate study. In the AM study, bimatoprost (n = 6) and NCX 470 (n = 6) were administered at the equimolar doses of 0.03% and 0.042%, respectively. Bimatoprost PM doses were 0.01% (n = 6) and 0.03% (n = 6), whereas NCX 470 PM doses were 0.014% (n = 6), 0.042% (n = 6), and 0.065% (n = 6).

In experiments in which the IOP-lowering effects of NCX 470 were evaluated after repeated dosing, NCX 470 (0.042%, 30 μL) or the respective vehicle was administered daily for 4 consecutive days (PM dosing) 18 and 24 hours before the IOP recordings were taken. One topical drop of proparacaine HCl 0.13% was applied to the eye before IOP readings in all experiments.

**Ocular Hypertensive Nonhuman Primates.** Eight female cynomolgus monkeys between the ages of 4 and 15 years were included in each study. Between 0.2 and 8.3 years prior to the study, all animals had unilateral laser treatment to the trabecular meshwork (TM) of the left eye to raise the IOP at least 5 mm Hg more than the right eye. In these animals, the IOP elevation persisted indefinitely to produce a chronic glaucoma model. Intraocular pressure measurements were made on 2 separate days 3 days apart. Bottles were masked and labeled A or B. One bottle contained NCX 470 at 0.042%, and the paired bottle contained bimatoprost at equimolar concentration (0.03%) in head-to-head studies. Drug testing was performed only in lesioned ocular hypertensive eyes. Intraocular pressure readings were taken by an experienced investigator blind to the treatment at 0 (baseline), 2, 4, 6, and 24 hours post AM dosing or at 0 (baseline), 12, and 18 hours post PM dosing in a separate study. Animals were scated in specially designed chairs for all conscious tonometry measurements. One topical drop of proparacaine HCl 0.13% was applied to the eye, and readings were made using a pneumotonometer (Model 30). All data were saved and analyzed later.

### RESULTS

**NCX 470, Bimatoprost, Bimatoprost-Free Acid, and cGMP Levels in Ocular Tissues Following Topical NCX 470 and Bimatoprost in Pigmented Dutch Belted Rabbits**

NCX 470, bimatoprost, and bimatoprost acid levels were determined to compare ocular exposure of NCX 470 and bimatoprost following topical dosing in pigmented Dutch Belted rabbits. Levels of cGMP were determined as a surrogate marker for NO release in ocular target tissues. More specifically, we determined the levels of NCX 470, bimatoprost, and bimatoprost acid in rabbit CR, AH, and ICB as well as those of cGMP in AH and ICB following topical administration of NCX 470 (30 μL, 0.042%) or bimatoprost (30 μL, 0.03%). Little or no intact NCX 470 or bimatoprost was detected in ocular tissues (levels were below the limit of quantitation, data not shown). Bimatoprost acid was the major species detected.
and thus used to evaluate potential differences in drug exposure between NCX 470 and bimatoprost.

As shown in Table 1 and Figures 1A and 1B, the levels of bimatoprost acid reached 60.2 ± 15.1 ng/g tissue, 139.0 ± 57 ng/mL, and 555 ± 204 ng/g tissue, respectively, in ICB, AH, and CR after NCX 470 (0.042%) treatment.

However, albeit not significantly, bimatoprost acid tended to be higher following NCX 470 treatment than after equimolar bimatoprost treatment.

Basal cGMP levels were 9.4 ± 0.7 pmol/g tissue and 9.3 ± 2.0 pmol/mL, respectively, in ICB and AH. Instillation of NCX 470 (30 μL, 0.042%) increased the levels of cGMP over time in both ocular compartments compared to pretreatment values (Fig. 2). In both tissues, maximum levels were detected at 18 and 24 hours post NCX 470 dosing (28.6 ± 1.1 and 24.8 ± 4.6 pmol/g tissue in ICB at 18 and 24 hours, respectively; 18.0 ± 2.3 and 23.9 ± 1.0 pmol/mL in AH at 18 and 24 hours, respectively).

**NCX 470 and Bimatoprost IOP-Lowering Activity in Transiently Ocular Hypertensive New Zealand White Rabbits**

We and others have repeatedly reported that tOHT-rabbits are sensitive to most IOP-lowering agents including NO17 but not to PGF2α agonists,13,18,19 which makes this species ideal to dissect out the NO-mediated effects of NCX 470. Hypertonic saline injection (0.1 mL) into the vitreous body transiently increased IOP from 18.7 ± 0.4 to 46.7 ± 1.4 mm Hg within 30 minutes to then gradually return back to baseline over the following 5 hours (Fig. 3A). The administration of NCX 470 (0.042%) or bimatoprost (0.03%) resulted in moderate, not significant, IOP lowering versus vehicle (data not shown). However, NCX 470 administered at 0.14% significantly blunted the IOP rise throughout the experimental period in this model. The effect was likely due to NO release, as bimatoprost at an equimolar dose (0.1%) did not lower IOP (Figs. 3A, 3B).

**NCX 470 and Bimatoprost IOP-Lowering Activity in Ocular Normotensive Dogs Following Single and Repeated Daily Dosing**

The IOP-lowering activity of NCX 470 (0.042%, 30 μL, AM dosing) was compared to that of an equimolar dose (0.03%, 30 μL, AM dosing) of bimatoprost at 2, 4, 6, and 24 hours post dosing in ONT-dogs. The IOP-lowering effect of bimatoprost and NCX 470 in ONT-dogs tended to increase over time to reach a steady state between 6 and 24 hours (Table 2). NCX 470 was generally more efficacious than bimatoprost, and the difference reached significance at 2 and 24 hours post dosing (Table 2). We next studied the IOP-lowering effect of different PM doses of NCX 470 at 12 and 18 hours post dosing in this model. Prior to treatment, baseline IOP readings did not differ between groups (Table 3). Topical administration of NCX 470 at 0.014%, 0.042%, and 0.065% (30 μL, PM dosing) dose-dependently reduced IOP at 12 and 18 hours post dosing (Table 3). A similar dose-response profile was observed after bimatoprost administration at equimolar doses. However, the IOP-lowering efficacy of NCX 470 was greater than that of equimolar bimatoprost at all tested time points (Table 3). We next determined whether the IOP-lowering effects of NCX 470 were retained over repeated treatments. For this purpose normotensive dogs were dosed once daily for 4 consecutive days with 0.042% (30 μL, PM dosing) NCX 470 or the
3.6 mm Hg in nonhuman primates. Intraocular pressure change versus baseline was calculated as follows: \( \text{IOP}_{\text{change}} = \text{IOP}_{\text{t}} - \text{IOP}_{\text{b}} \), where \( \text{IOP}_{\text{t}} \) and \( \text{IOP}_{\text{b}} \) are respectively the IOP at the indicated time points and prior to dosing. Data are presented as mean ± SEM, mm Hg, \( n = 6 \).

### NCX 470 and Bimatoprost IOP-Lowering Activity in Laser-Induced Ocular Hypertensive Nonhuman Primates

Similar to studies in ONT-dogs, efficacy studies in ocular hypertensive OHT-monkeys were initially conducted to address the IOP-lowering activity of AM dosing of NCX 470 (0.042%, 30 μL) or equimolar (0.03%, 30 μL) bimatoprost. Measurements were recorded prior to dosing the animals (baseline) and 2, 4, 6, and 24 hours thereafter. In OHT-monkeys, both compounds were progressively effective to reach the maximum IOP-lowering activity between 6 and 24 hours post dosing. In this set of experiments, NCX 470 was more active than bimatoprost at 4, 6, and 24 hours post dosing (Table 2). In a second set of experiments, the IOP-lowering efficacy of PM dosing of NCX 470 (0.042%, 30 μL) and bimatoprost (0.03%, 30 μL) was assessed at 12 and 18 hours post dose. Baseline IOP readings did not differ significantly between eyes later assigned to the two treatments (Fig. 5). Topical instillation of NCX 470 (0.042%, 30 μL, \( n = 6 \)) led to a more pronounced IOP reduction than equimolar doses of bimatoprost (0.03%, 30 μL). Specifically, NCX 470 significantly decreased IOP at 12 and 18 hours post dosing relative to baseline by 22.5 ± 3.2% and 24.2 ± 3.4%, respectively (Fig. 5). Bimatoprost was significantly effective compared to baseline (%IOP reduction, 8.6 ± 3.9% and 13.3 ± 3.2% at 12 and 18 hours post dosing, respectively) but less active than NCX 470 (Fig. 5).

### DISCUSSION

NCX 470 is an NO-donating bimatoprost carrying an NO moiety esterified with the hydroxyl group present in position 15 of the bimatoprost structure. NCX 470 was effective in lowering IOP in tOHT-rabbits as well as in ONT-dogs and nonhuman primates with unilateral laser-induced ocular hypertension (OHT-monkeys). Furthermore, repeated daily dosing of NCX 470 in ONT-dogs resulted in sustained IOP-lowering activity over time. The administration of NCX 470 to tOHT-rabbits diminished the transient ocular hypertensive response elicited by the intravitreal injection of hypertonic saline. The effect in tOHT-rabbits was likely dependent from the release of NO in target tissues rather than the bimatoprost moiety (i.e., bimatoprost and bimatoprost acid), as bimatoprost itself was inactive in this model. In line with this conclusion, previous reports documented that NO donors are effective IOP-lowering agents in rabbits\(^\text{17}\) while this species is virtually nonresponsive to PGF\(_2\alpha\) analogues such as latanoprost.\(^\text{15,17,18,20}\) In ONT-dogs, NCX 470 progressively lowered IOP to reach its maximum effects between 6 and 24 hours post dosing. At most time points tested, NCX 470 lowered IOP more than equimolar bimatoprost. In ONT-dogs, NCX 470 tested at doses ranging from 0.014% to 0.065% lowered IOP at 12 and 18 hours in a dose-dependent fashion. The effects were generally

### Table 3. NCX 470 and Bimatoprost IOP-Lowering Activity in ONT-Dogs Following Ocular PM Topical Dosing

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose, %</th>
<th>Average Basal IOP, mm Hg</th>
<th>IOP Change vs. Baseline at 12 h Post Dosing, mm Hg</th>
<th>IOP Change vs. Baseline at 18 h Post Dosing, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCX 470</td>
<td>0.014</td>
<td>18 ± 2</td>
<td>-4.8 ± 0.5(^*)</td>
<td>-4.7 ± 0.4(^*)</td>
</tr>
<tr>
<td></td>
<td>0.042</td>
<td>20 ± 3</td>
<td>-5.7 ± 0.7(^*)</td>
<td>-5.4 ± 0.7(^*)</td>
</tr>
<tr>
<td></td>
<td>0.065</td>
<td>19 ± 2</td>
<td>-6.6 ± 0.6</td>
<td>-5.7 ± 1.0</td>
</tr>
<tr>
<td></td>
<td>0.030</td>
<td>20 ± 3</td>
<td>-3.2 ± 0.9</td>
<td>-3.4 ± 0.7</td>
</tr>
<tr>
<td>Bimatoprost</td>
<td>0.010</td>
<td>18 ± 1</td>
<td>-2.1 ± 0.5</td>
<td>-1.3 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>0.030</td>
<td>20 ± 3</td>
<td>-3.2 ± 0.9</td>
<td>-3.4 ± 0.7</td>
</tr>
</tbody>
</table>

Drugs were administered at the indicated dose dissolved in 30 μL vehicle containing 0.25% Tween-80, 0.02% BAK, 2% glycerin, and 0.1% EDTA. Intraocular pressure change versus baseline was calculated as follows: \( \text{IOP}_{\text{change}} = \text{IOP}_{\text{t}} - \text{IOP}_{\text{b}} \), where \( \text{IOP}_{\text{t}} \) and \( \text{IOP}_{\text{b}} \) are respectively the IOP at the indicated time points and prior to dosing. Data are presented as mean ± SEM, mm Hg, \( n = 6 \).

\(^*\) \( P < 0.05 \) versus bimatoprost at the respective equimolar dose.
Comparison between treatments was performed using a mixed model ANOVA analysis incorporating animal-to-animal and period-to-period variability.

Greater than those elicited by equimolar doses of bimatoprost. On average, NCX 470 was approximately three times more potent than bimatoprost, as the 0.014% dose of NCX 470 was as effective as the 0.03% dose of bimatoprost in this model. Repeated daily dosing of NCX 470 at 0.042% resulted in sustained IOP lowering over time without appreciable eye redness or general discomfort as assessed by visual inspection before and after dosing the animals, suggesting that this compound is largely safe and well tolerated in ONT-dogs. However, additional studies are needed to better address the safety profile of this compound.

In unilateral OHT-monkeys, NCX 470 effectively controlled IOP following AM dosing at 2, 4, 6, and 24 hours post dose. Furthermore, when tested head-to-head with equimolar PM doses of bimatoprost, NCX 470 was a more effective IOP-lowering agent compared to bimatoprost, confirming the additional IOP-lowering contribution exerted by NO as in previous work performed with compounds that release NO under similar experimental conditions. While more investigation is needed to understand the potential contribution of this alternative pathway, independent lines of investigation consistently reported on the ability of NO to relax TM and Schlemm’s canal (SC) that ultimately results in enhanced trabecular outflow facility.9,15 Furthermore, NO seems to also affect AH formation at the ciliary epithelium.6 Both these effects are mediated via soluble guanylyl cyclase activation and cGMP formation.26,27 NCX 470 treatment released NO in target ocular tissues. Bimatoprost and bimatoprost acid (the latter being released from bimatoprost via the action of amiodopépídase21) are also the active molecular species following bimatoprost treatment.22 It is known, however, that rabbits, more than higher species, rapidly hydrolyze bimatoprost to bimatoprost acid.21 In our study, the levels of bimatoprost in rabbit AH, CR, and ICB were equally low following NCX 470 or bimatoprost dosing, making any meaningful conclusion on the contribution of this molecule in the overall IOP-lowering activity of these compounds in our experimental conditions difficult. On the other hand, the levels of bimatoprost acid were measurable and were found slightly increased in target ocular tissues of rabbits exposed to NCX 470 compared to equimolar concentrations of bimatoprost. It is possible that part of the superior IOP-lowering effects of NCX 470 might be due to a greater bimatoprost acid exposure following NCX 470 administration. Bimatoprost exerts its IOP-lowering effects mainly by activating FP receptors23,24 with a minor contribution coming from EP3 receptors.25 It is possible that minor changes in bimatoprost acid exposure resulting from NCX 470 could have enhanced the EP3 contribution and thus the overall IOP decrease observed with this drug compared with that of bimatoprost. Additional experiments are needed to further understand the potential contribution of this alternative pathway. Intraocular pressure (IOP) in ocular normotensive beagle dogs (ONT-dogs) after instillation of NCX 470 (0.042%, open circle) and its respective vehicle (closed triangle, 0.25% Tween-80; 0.02% BAK, 2% glycerin, and 0.1% EDTA). NCX 470 was administered daily between 2 and 3 PM for 4 consecutive days at the indicated concentration in one eye, whereas the contralateral eye received the respective vehicle (30 μL). Data are reported as mean ± SEM, n = 6. *P < 0.05 versus respective vehicle. Comparison between treatments was performed using a mixed model ANOVA analysis incorporating animal-to-animal and period-to-period variability.

FIGURE 4. NCX 470 and bimatoprost IOP-lowering activity in ocular normotensive dogs (ONT-dogs) following repeated daily dosing. Intraocular pressure (IOP) in ocular normotensive beagle dogs (ONT-dogs) after instillation of NCX 470 (0.042%, open circle) and its respective vehicle (closed triangle, 0.25% Tween-80; 0.02% BAK, 2% glycerin, and 0.1% EDTA). NCX 470 was administered daily between 2 and 3 PM for 4 consecutive days at the indicated concentration in one eye, whereas the contralateral eye received the respective vehicle (30 μL). Data are reported as mean ± SEM, n = 6. *P < 0.05 versus respective vehicle. Comparison between treatments was performed using a mixed model ANOVA analysis incorporating animal-to-animal and period-to-period variability.

FIGURE 5. NCX 470 and bimatoprost IOP-lowering activity in laser-induced ocular hypertensive nonhuman primates (OHT-monkeys). Intraocular pressure (A) and changes from baseline (B) in unilateral laser-induced ocular hypertensive cynomolgus OHT-monkeys after the instillation of NCX 470 (0.042%, open circle) or bimatoprost (0.03%, closed circle). IOP change versus baseline was calculated as follows: (Drug IOPt − Drug IOP0)/Drug IOP0 where IOPt and IOP0 are, respectively, the IOP at the time of interest and prior to dosing. Data are reported as mean ± SEM, n = 6. *P < 0.05 versus bimatoprost at the respective time points post dosing.
IOP-Lowering of NCX 470, a NO-Donating Bimatoprost

leading to reduced AH humor formation at the ciliary processes and enhanced AH drainage via TM and SC.7,27

In summary, NCX 470 is a novel compound endowed with two mechanisms of action that cooperate to lower AH production and improve trabecular outflow facility as well as increase uveoscleral outflow. The superior IOP-lowering activity of NCX 470 compared to bimatoprost is likely attributed to NO release, even if marginal changes in bimatoprost acid exposure of ocular target tissues could have also contributed.

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