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Monograph

NCX-470

Nitric oxide-donating prostaglandin analogue
Treatment of glaucoma
Treatment of ocular hypertension

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Summary

Glaucoma is a disease affecting millions of people across the world every year. Medications designed to control or decrease intraocular pressure are the gold standard for treatment and often belong to a class of medications called prostaglandin analogues. These topical agents are well tolerated and alleviate intraocular pressure by inducing the flow of aqueous humor through the interstitial spaces of the ciliary muscle. A novel medication with potential for increased efficacy in intraocular pressure reduction is needed for glaucoma treatment, and evidence is mounting for the new class of nitric oxide-donating prostaglandins to achieve this task. This review aims to present and discuss the evidence pertaining to NCX-470, a nitric oxide-donating prostaglandin.

Key words: *NCX-470 – Bimatoprost – Nitric oxide – Prostaglandin analogue – Intraocular pressure – Open-angle glaucoma – Ocular hypertension*

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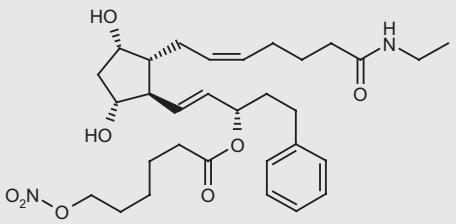
*Synthesis prepared by V. Carceller, Clarivate, Barcelona, Spain.



15-*O*-(6-Nitrooxyhexanoyl)-17-phenyl-18,19,20-trinorprostaglandin F2α *N*-ethylamide

InChI=1S/C31H46N2O8/c1-2-32-30(36)16-10-4-3-9-15-26-27(29(35)23-28(26)34)21-20-25(19-18-24-13-7-5-8-14-24)41-31(37)17-11-6-12-22-40-33(38)39/h3,5,7-9,13-14,20-21,25-29,34-35H,2,4,6,10-12,15-19,22-23H2,1H3,(H,32,36)/b9-3-,21-20+/t25-,26+,27+,28-,29+/m0/s1

$C_{31}H_{46}N_2O_8$; Mol wt: 574.706

Cortellis Drug Discovery Intelligence Entry Number: 680093

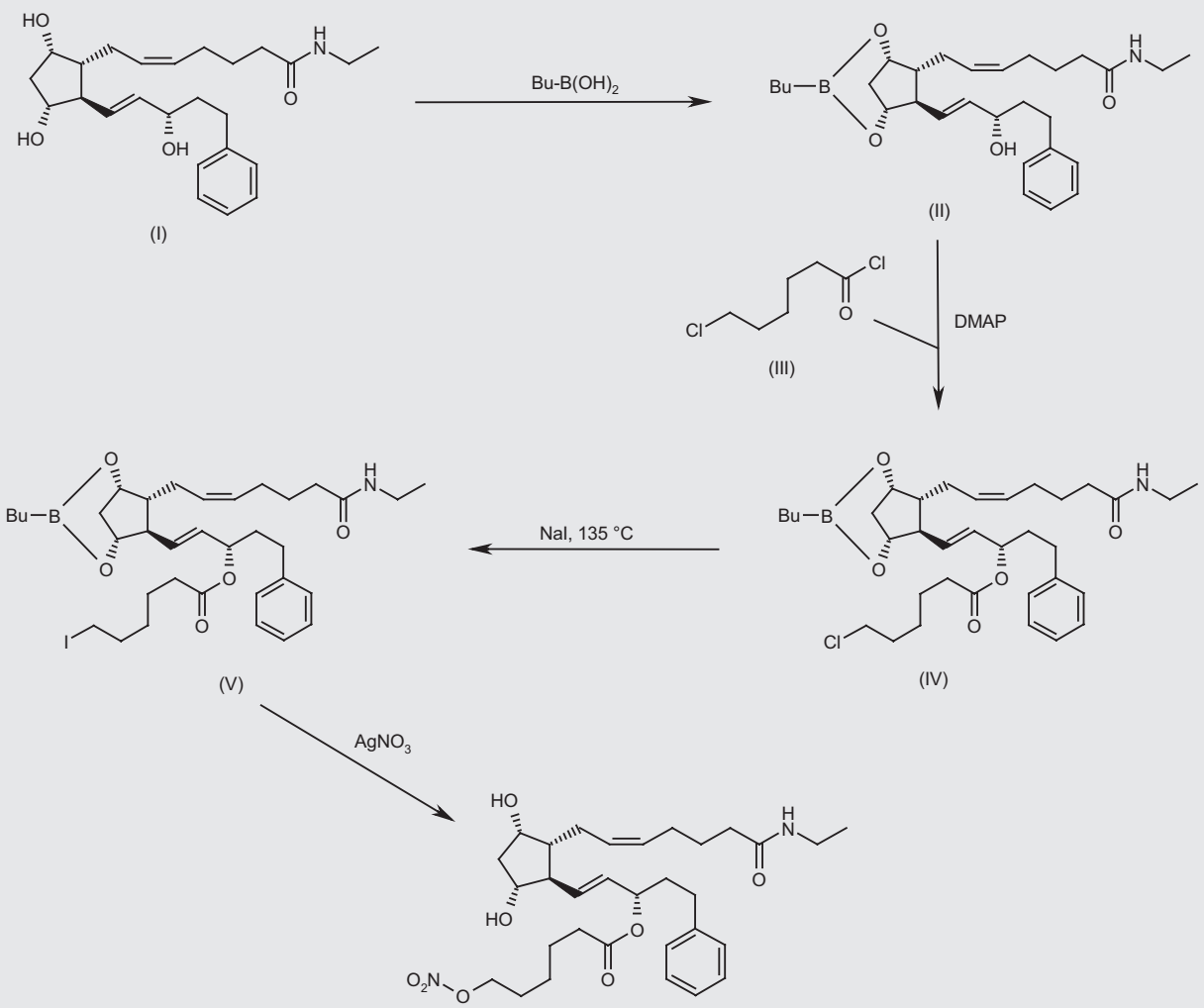
Synthesis*

NCX-470 can be obtained by 2 related methods:

1) Reaction of bimatoprost (I) with butylboronic acid in CH_2Cl_2 or MTBE gives boronate (II) (1-3), which is then condensed with 6-chlorohexanoyl chloride (III) in the presence of DMAP in CH_2Cl_2 to yield ester (IV). Displacement of chloride (IV) with NaI in acetone at 135 °C provides iodo compound (V), which is finally nitrated with $AgNO_3$ in acetonitrile (1). Scheme 1.

2) Ring opening of oxepan-2-one (VI) with KOH in MeOH produces potassium 5-carboxypentan-1-olate (VII), which upon nitration with HNO_3 in the presence of H_2SO_4 in CH_2Cl_2 at 5 °C yields nitro compound (VIII). Chlorination of 6-(nitrooxy)hexanoic acid (VIII) with $(COCl)_2$ in the presence of DMF in CH_2Cl_2 gives acid chloride (IX), which is then coupled with alcohol (II) using DMAP in CH_2Cl_2 to furnish the corresponding ester (X).

Scheme 1. Synthesis of NCX-470



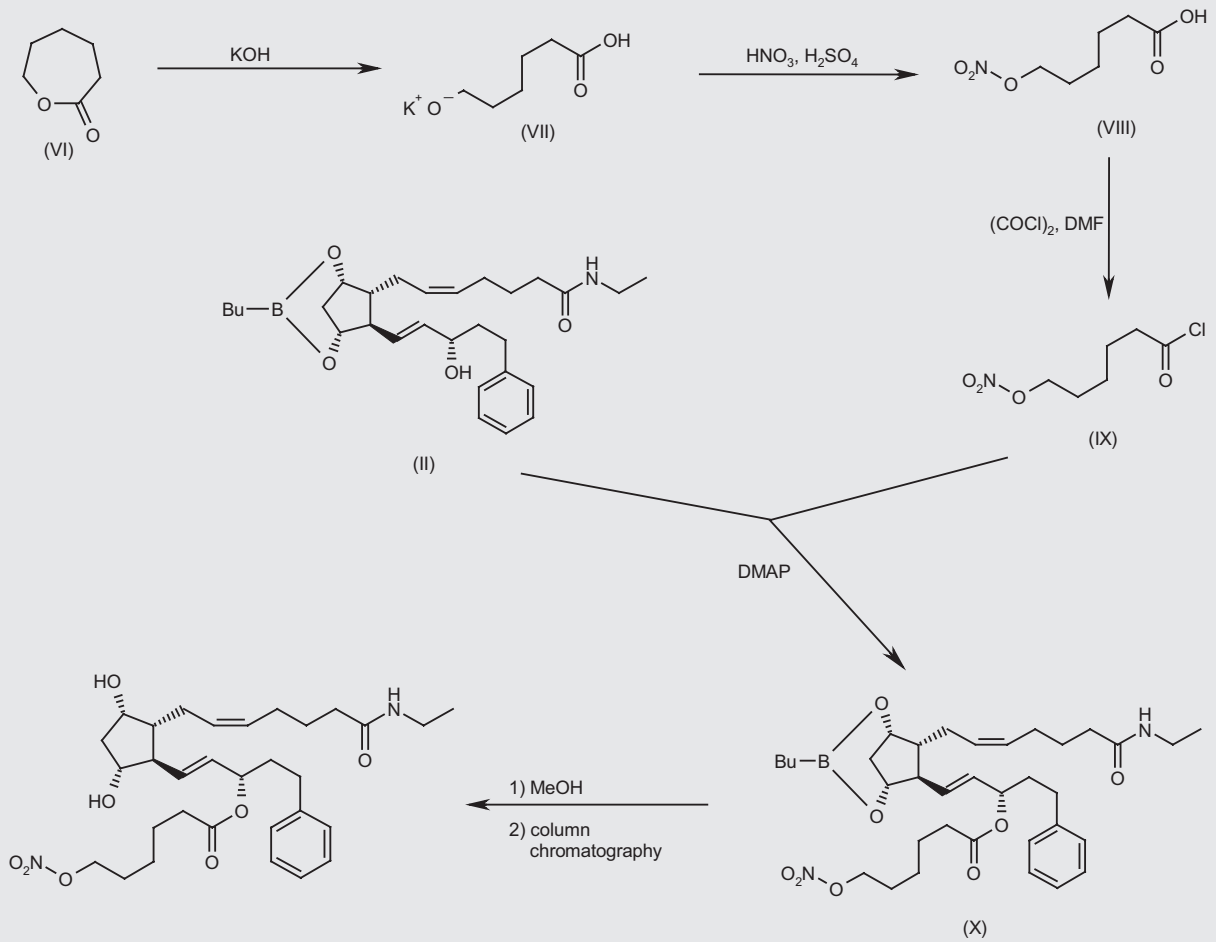
Finally, compound (X) is deprotected using MeOH, followed by enrichment of product purity using column chromatography (2, 3). Scheme 2.

Background

Glaucoma is a progressive ocular disease that is the leading cause of blindness in the United States (4). The number of people diagnosed with glaucoma is increasing, with an estimated 76 million people affected in 2020 and a worldwide prevalence rate of 3.54% for adults between 40 and 80 years of age (5). Glaucoma presents a large economic burden in the United States; it is estimated that about $2.9 billion is spent on treating glaucoma each year (6). Additionally, the financial burden of glaucoma increases with disease progression, and patients with advanced-stage glaucoma spend, on average, $2,511 in direct annual costs primarily related to medication expenditures in the United States (6).

There are a number of risk factors for glaucoma including family history, elevated intraocular pressure, a thin central cornea, advancing age, myopia, history of ocular trauma and pseudoexfoliation (4). Open-angle glaucoma, the most common form of the disease, is marked by optic nerve damage, structural changes to the optic disk, and damage or destruction of retinal ganglion cells (7). If untreated, open-angle glaucoma can greatly reduce the visual field. According to the American Academy of Ophthalmology, previous studies have established a link between intraocular pressure (IOP) and open-angle glaucoma (8). While IOP has previously been used as a diagnostic marker of glaucoma, the susceptibility of the optic nerve to damage caused by elevated IOP varies greatly between patients (8).

Scheme 2. Synthesis of NCX-470



The primary method of treatment for open-angle glaucoma involves management of the patient's IOP through application of topical solutions, followed by laser or incisional surgery if required (8). The most prescribed class of medications used to lower IOP is the prostaglandin analogues, whose agents are often preferred as they are generally well tolerated and have desired frequency of being administered once daily (8). This class of medications acts primarily by inducing the uveoscleral, or unconventional, outflow pathway, the flow of aqueous humor through the interstitial spaces of the ciliary muscle into the suprachoroidal space (9). Additionally, topical β-adrenergic antagonists, either nonselective or β_1-selective, which lower IOP through reduction of aqueous humor formation are frequently prescribed (8). Other indicated therapies including α_2-adrenergic agonists, parasympathomimetic agents, carbonic anhydrase inhibitors, and Rho kinase inhibitors are administered individually or in fixed combination formulations and function through mechanisms that target uveoscleral outflow, trabecular outflow, aqueous humor production or episcleral venous pressure (8, 10). The current treatment options for IOP reduction are listed in Table I.

Despite a variety of available pharmacotherapies, IOP control in open-angle glaucoma and ocular hypertension is often challenging, as mechanistic limitations of traditional agents preclude individualized care and result in refractory patient response. Concomitant administration typically improves therapeutic efficacy but may become inconvenient, uncomfortable or costly to patients and ultimately impair adherence.

A number of novel agents utilize versatile mechanisms of action with the potential to address needs in open-angle glaucoma and ocular hypertension management. Nitric oxide (NO)-donating derivatives of prostaglandin analogues, phosphodiesterase 5 (PDE5) inhibitors, β-adrenergic antagonists, carbonic anhydrase inhibitors, Rho kinase inhibitors and other compounds comprise classes of agents in recent or current development and postmarketing stages (11-14).

Table I. *Current treatments for intraocular pressure reduction.*

Medication name (Ref.)	Medication category	Mean IOP reduction	Dosage	Mechanism of action
NCX-470 (22)	NO-donating prostaglandin analogue	7.6-9.8 mmHg[a]	0.065% or 0.1% once daily[b]	Increasing uveoscleral and trabecular meshwork outflow
Latanoprost (Xalatan) (25)	Prostaglandin $F_{2\alpha}$ analogue	6-8 mmHg	0.05 mg/mL once daily	Increasing uveoscleral outflow
Travoprost (Travatan Z) (26)	Synthetic prostaglandin F analogue	7-8 mmHg	0.04 mg/mL once daily	Increasing uveoscleral outflow
Tafluprost (Zioptan) (27)	Fluorinated prostaglandin $F_{2\alpha}$ analogue	6-8 mmHg	0.015 mg/mL once daily	Increasing uveoscleral outflow
Bimatoprost (Lumigan) (28)	Synthetic prostaglandin $F_{2\alpha}$ analogue	7-8 mmHg	0.3 mg/mL once daily	Increasing uveoscleral and trabecular meshwork outflow
Latanoprostene bunod (Vyzulta) (17)	NO-donating prostaglandin analogue	7-9 mmHg	0.24 mg/mL once daily	Increasing uveoscleral and trabecular meshwork outflow
Timolol maleate (Istalol) (29)	Nonselective β-adrenergic receptor blocking agent	6-7 mmHg	5 mg/mL once daily	Reducing aqueous humor production
Brimonidine (Alphagan P) (30)	Relatively selective α_2-adrenoceptor agonist	2.6-4.3 mmHg	0.15% w/v 3 times daily	Reducing aqueous humor production and increasing uveoscleral outflow
Apraclonidine (Iopidine) (31)	Relatively selective α_2-adrenoceptor agonist	3.7-5.0 mmHg	0.5% w/v 3 times daily	Reducing aqueous humor production and increasing uveoscleral outflow
Dorzolamide hydrochloride (Trusopt) (32)	Carbonic anhydrase inhibitor	3-5 mmHg	20 mg/mL 3 times daily	Decreased aqueous humor secretion
Brinzolamide (Azopt) (33)	Carbonic anhydrase inhibitor	4.1-5.6 mmHg	10 mg/mL 3 times daily	Decreased aqueous humor secretion
Netarsudil (Rhopressa) (34)	Rho kinase inhibitor	4-5 mmHg	0.02% once daily	Increase outflow of aqueous humor through trabecular meshwork
Netarsudil/ latanoprost (Rocklatan) (35)	Rho kinase inhibitor/ prostaglandin $F_{2\alpha}$ analogue	9.5 mmHg	0.02%/0.005% once daily	Increase outflow of aqueous humor

[a]Based on the phase II data of 0.065% NCX-470.
[b]Currently being evaluated for the target dose.

Among these, NO-donating prostaglandin analogues are the first and only class commercially available for the treatment of open-angle glaucoma and ocular hypertension in the United States. The conventional or trabecular outflow pathway, the primary pathway for the flow of aqueous humor out of the eye, is generally unaffected by traditional prostaglandin analogues, but NO-donating prostaglandin analogues may induce this pathway and present robust, synergistic mechanisms of IOP control (9).

Latanoprostene bunod (LBN), a NO-donating derivative of a prostaglandin $F_{2\alpha}$ agonist ($PGF_{2\alpha}$) known as latanoprost, received FDA approval in 2017 following the APOLLO and LUNAR studies of LBN 0.024% vs. timolol maleate 0.5% in patients with open-angle glaucoma or ocular hypertension (15, 16). In both studies, baseline mean IOP was similar among treatment arms, and LBN demonstrated superiority to timolol in IOP change from baseline at most time points measured within the 3-month efficacy study periods. At time points measured during weeks 2, 6 and 12, IOP measurements in the LBN arms were significantly lower than those of comparative timolol arms, with adjusted treatment differences ranging from −0.4 to −1.4 mmHg ($P < 0.001$ to 0.216), −0.8 to −1.3 mmHg ($P < 0.001$ to 0.007), and −0.9 to −1.3 mmHg ($P < 0.001$ to 0.006), respectively (15-17).

The success of LBN as a first-in-class agent has since encouraged investigation of alternative prostaglandin analogues with NO moieties. In 2020, Nicox Ophthalmics initiated phase III studies of NCX-470, a NO-donating derivative of the $PGF_{2\alpha}$ agonist bimatoprost (18, 19). Current studies compare the effects of NCX-470 0.065% and NCX-470 0.1% vs. latanoprost 0.005% on IOP in patients with open-angle glaucoma and ocular hypertension. Considering the established efficacy of bimatoprost in IOP control along with promising early-phase data, coming phase III results may establish NCX-470 as the first noncombination antiglaucoma agent with demonstrated statistical superiority to a traditional

prostaglandin analogue (9, 20). Moreover, approval of this additional, mechanistically diverse antiglaucoma treatment may advance approaches to IOP management and improve long-term patient outcomes.

Preclinical Pharmacology

A study by Impagnatiello et al. investigated the IOP-lowering effects of NCX-470 against equimolar doses of bimatoprost in New Zealand white rabbits with transient hypertonic saline-induced IOP elevation, cynomolgus primates with laser-induced ocular hypertension and normotensive beagles. Specifically, New Zealand white rabbits are known to be responsive to NO but are relatively less responsive to $PGF_{2\alpha}$ analogues and were therefore chosen to ascertain the impact of NO administration on glaucoma. In transiently ocular hypertensive (tOHT) rabbits who received NCX-470 0.14%, IOP was maximally lowered by −7.2 ± 2.8 mmHg at 90 min post dose. In ocular normotensive (ONT) dogs, NCX-470 0.042% had increased efficacy compared to equimolar bimatoprost, with a pressure lowering of −5.4 ± 0.7 vs. −3.4 ± 0.7 mmHg. In OHT monkeys, NCX-470 similarly decreased IOP by −7.7 ± 1.4 vs. −4.8 ± 1.7 mmHg 18 h after dosing (21).

It was found that NCX-470 lowered the IOP more than bimatoprost in each of these species via a dual mechanism of activation of the $PGF_{2\alpha}$, which increases uveoscleral outflow and NO-signaling pathways, thereby modulating the production and drainage of aqueous humor. This dual mechanism of $PGF_{2\alpha}$ activation and NO delivery may permit the use of lower doses compared to bimatoprost, which commonly causes eye redness as well as alterations in eye pigmentation and eyelash length (21).

Relaxation of Schlemm's Canal and the trabecular meshwork induced by NO causes increased trabecular outflow and mediates aqueous humor formation, both of which are modulated by soluble guanylyl cyclase activation and cGMP production. As cGMP levels in the trabecular meshwork are dependent on the expression and activity of the multidrug resistance-associated protein 4 (MRP-4) transport, MRP-4 inhibition by NCX-470 or the moieties it releases may contribute to increased cGMP levels. It has been further hypothesized that minor changes in bimatoprost acid exposure as a result of NCX-470 administration enhance activation of EP_3, a prostanoid receptor at which activation inhibits the production of adenylyl cyclase and may contribute to greater IOP-lowering activity compared to bimatoprost (21).

Furthermore, in the preclinical study by Impagnatiello et al., levels of either NCX-470 or bimatoprost in addition to bimatoprost acid were quantified in the aqueous humor, cornea and iris/ciliary body in male pigmented Dutch Belted rabbits to examine the medication absorption post dose. Levels of cGMP in the aqueous humor and iris/ciliary body following administration of 30 µL of either NCX-470 0.042% or bimatoprost 0.03% into both eyes were also measured. Upon quantification, bimatoprost acid was the major species detected in all specimens, with no intact NCX-470 or bimatoprost identified, and was therefore used to determine potential differences in drug exposure. Following dosing, levels of bimatoprost acid rose to 60.2 ± 15.1 ng/g tissue, 139.0 ± 37 ng/mL and 555 ± 204 ng/g tissue in the iris/ciliary body, aqueous humor and cornea. Additionally, cGMP levels increased to maximum values of 28.6 ± 1.1 and 24.8 ± 4.6 pmol/g tissue in the iris/ciliary body, and 18.0 ± 2.3 and 23.9 ± 1.0 pmol/mL in the aqueous humor at 18 and 24 h post dose with NCX-470 (21).

In normotensive beagles, it was found that NCX-470 released NO in ocular tissue, as indicated by the accumulation of cGMP in the aqueous humor and iris/ciliary body. For both NCX-470 0.03% and bimatoprost 0.042%, the observed pressure-lowering effects increased to achieve steady state between 6 and 24 h after dosing, with NCX-470 achieving significant improvements in efficacy compared to bimatoprost at 2 and 24 h post dosing. Administration of NCX-470 at strengths of 0.014%, 0.042%, and 0.065% also reduced IOP in a dose-dependent manner at 12 and 18 h post dosing. While bimatoprost exhibited similar effects, the efficacy of NCX-470 was superior at all time points. The dogs were later dosed for 4 consecutive days using once-daily dosing of 0.042% NCX-470 in the evening. IOP was measured twice daily during the treatment period, and it was shown that NCX-470 maintained its pressure-lowering effects throughout the duration of treatment (21).

In tOHT New Zealand white rabbits, NCX-470 0.14% or bimatoprost 0.1% was administered into each eye following injection of hypertonic saline into the vitreous body. While the administration of both NCX-470 and bimatoprost at lower concentrations did not significantly decrease IOP, NCX-470 0.14% significantly impaired the pressure increase. As bimatoprost at an equimolar dose did not significantly lower the pressure, it is hypothesized that the observed effect is a result of NO release by NCX-470 (21).

NCX-470 0.042% or bimatoprost 0.03% was also administered to OHT nonhuman primates that underwent unilateral laser treatment to the trabecular meshwork of the left eye to increase IOP. With both treatments, there was progressive pressure lowering with maximum lowering between 6 and 24 h after dosing. NCX-470 was more active than bimatoprost at 4, 6 and 24 h post dosing. Using evening dosing, NCX-470 resulted in a more marked pressure reduction than bimatoprost. NCX-470 significantly reduced pressure at 12 and 18 h post dosing compared to baseline by 22.5 ± 3.2% and 24.2 ± 3.4% while bimatoprost was less effective with a pressure reduction of 8.6 ± 3.9% and 13.3 ± 3.2% (21).

Clinical Evaluation

Dolomites, a phase II, randomized, dose-response study evaluated the safety and efficacy of NCX-470 in subjects with

diagnoses of ocular hypertension or open-angle glaucoma in both eyes at 3 concentrations. Participants were 18-85 years of age and were randomized to receive NCX-470 at 3 doses, 0.021%, 0.042% and 0.065% or latanoprost 0.005% ophthalmic solution. For 27 days, 433 subjects received doses of NCX-470 or latanoprost once daily in the evening and were assessed for difference in treatment effect measured by mean diurnal IOP change from baseline between each dose. Means for alterations in daytime IOP were compared to baseline IOP on day 28 for 0.021%, 0.042% or 0.065% NCX-470 or 0.005% latanoprost and a noninferiority analysis was performed for the results of each treatment, revealing that all doses of NCX-470 exhibited noninferiority to 0.005% latanoprost and that 0.042% and 0.065% concentrations were statistically superior. Additionally, NCX-470 0.065% demonstrated a more effective IOP-lowering effect from baseline in comparison to latanoprost at 8 a.m., 10 p.m. and 4 p.m. on day 28 ($P = 0.0214$, 0.0008 and 0.0015, respectively). On days 7, 14 and 28, the mean reductions in daytime IOP from baseline at all time points on each collection day were greater for 0.065% NCX-470 than 0.005% latanoprost (7.6-9.8 vs. 6.3-8.8 mmHg) (22). Results from this phase II study leave room for evaluating further IOP lowering at higher doses for NCX-470 (22, 23).

A phase III study, Mont Blanc, is a randomized, adaptive dose-selection study evaluating the safety and efficacy of 0.065% and 0.1% NCX-470 in lowering IOP in participants ages 18 to 84 years with ocular hypertension or open-angle glaucoma in both eyes. An estimated 670 patients will be randomized in a 1:1:1 ratio to either 0.065% or 0.1% NCX-470 or to 0.005% latanoprost. Subsequently, patients will be randomized in a 1:1 ratio to the assigned dose of NCX-470 or to 0.005% latanoprost. This study's primary outcome measure is mean IOP reduction from baseline at week 2, week 6 and at month 3 in the morning and afternoon (8 a.m. and 4 p.m.). Secondary outcome measures include mean daytime IOP reduction from baseline, drug-related adverse events (AEs) and rate of cessation of treatment (19). Nicox recently reported topline results from Mont Blanc in a press release stating that NCX-470 0.1% dosed daily met the primary objective of noninferiority to latanoprost 0.005%. NCX-470 lowered IOP from baseline by 8.0 to 9.7 mmHg compared to 7.1 and 9.4 mmHg for latanoprost. The secondary efficacy objective of statistical superiority to latanoprost was not achieved, but NCX-470 0.1% was statistically superior in IOP reduction at 4 of the 6 timepoints, and numerically greater at all 6 timepoints (24).

Another phase III study, Denali, is a 12-month randomized, multiregional study evaluating the safety and efficacy of 0.1% NCX-470 compared to 0.005% latanoprost in the same subject population, individuals aged 18-84 years with ocular hypertension or open-angle glaucoma. Eligibility requirements are identical to those of Mont Blanc, while the primary endpoint is alteration in IOP from baseline at week 2, week 6 and month 3. Patients will be randomized in a 1:1 ratio to receive either 0.1% NCX-470 or 0.005% latanoprost once daily in the evening, and the study will include an extension evaluating long-term safety (18). Results are expected to be available after 2024 (12, 24).

The results produced from both phase III studies will help determine the long-term drug profile of NCX-470 and its ability to serve as both an efficacious and safe IOP-lowering agent that can be used in the treatment of open-angle glaucoma and ocular hypertension.

Safety

Safety of NCX-470 in the preclinical model with tOHT rabbits, OHT monkeys and ONT dogs was assessed by visual inspection at the 0.042% dose and reported to cause no "appreciable eye redness or general discomfort." The study suggested that safety endpoints should be addressed at a later date and at a more extensive level (21).

Additionally, upon completion of the phase II study, it was noted that NCX-470 was generally well tolerated. Notably, there were no occurrences of treatment-related AEs nor systemic side effects stemming from treatment with NCX-470. However, documented AEs included 3 occurrences of discontinuation due to AEs. The majority of the AEs reported in the study were classified as mild, and the most frequently reported AE was conjunctival hyperemia. Conjunctival hyperemia was seen in 16.8% of patients treated with NCX-470 at 0.065% compared to 6.5% of patients treated with 0.005% latanoprost. At the 0.042% concentration, however, the percentage of patients who experienced conjunctival hyperemia was higher (22.2%) (22, 23). The ongoing phase III studies are expected to expand our understanding of the safety profile of NCX-470.

Conclusions

NCX-470 has shown promising safety and efficacy when compared to latanoprost as a novel agent for IOP lowering in patients with ocular hypertension or open-angle glaucoma. The mechanism comprising NO-donation provides a new pathway to reduce IOP with increased efficacy. Results from the phase III studies will provide further information on its potential benefits and addition to the treatments available for IOP reduction in patients with open-angle glaucoma.

Disclosures

The authors state no conflicts of interest.

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