NCX 667, a novel nitric oxide (NO) donor, lowers intraocular pressure (IOP) in ocular normotensive and hypertensive eyes of rabbits and non-human primates

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INTRODUCTION

- Nitric Oxide (NO) is an endogenous cell-signaling molecule of fundamental importance in the eye. [1,2]
- Under pathological conditions such as glaucoma, NO activity is impaired and it has been shown to play a role in the intraocular pressure (IOP) increase typically seen in glaucoma patients.[3-4]
- NO has been shown to lower IOP in various animal models and in humans.[2, 5-8]
- NO increases conventional outflow through the trabecular meshwork.[2,6]
- VESNEO™ (latanoprostene bunod), a new chemical entity thought to have a dual mechanism of action, PGF2α agonist and NO donor, showed promising IOP lowering in Phase 2 and Phase 3 clinical trials in patients with glaucoma or ocular hypertension.[9]

PURPOSE

- This study characterizes NCX 667, a novel NO donor, for IOP lowering efficacy in New Zealand white rabbit and non-human primate models of glaucoma.

METHODS

Ocular hypertensive rabbits

Male New Zealand white (NZW) rabbits were injected with 0.1 ml of hypertonic saline solution (5%) into the vitreous humor of both eyes. Vehicle (phosphate buffer pH 6.0+cremophor EL 5%+ DMSO 0.3%+BAC 0.2mg/ml) or NCX 667 at different doses was instilled immediately after saline injection. IOP was determined using a pneumatonometer (Model 30™ Reichert, Depew, NY, USA) prior to hypertonic saline injection (baseline) and during the following 4 hours post dosing. One topical drop of NOVESINA 0.4% (Novartis) was applied to the eye prior to each IOP measurement.

Similar IOP recording was used in ocular normotensive NZW rabbits prior to (baseline) and during the following 5 hours post dosing.

Ocular hypertensive non-human primates

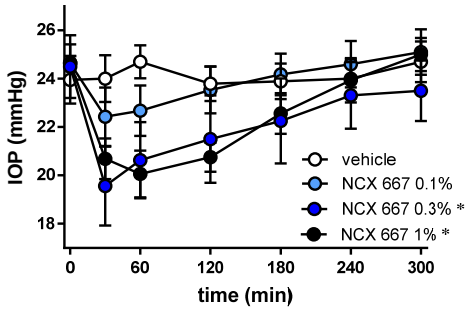
Female cynomolgus monkeys between 7 and 14 years old were included in the study. All had unilateral laser treatment to the trabecular meshwork (TM) of the left eye. Baseline IOP was measured the day before dosing while drug-mediated IOP changes were determined by comparing vehicle and treatment groups before dosing and during the following 5 hours. One topical drop of proparacaine HCl 0.13% was applied to the eye and measurements were made with a pneumatonometer.

Statistical analysis

Data are expressed as mean ± SEM. A *P*-value of <0.05 was considered significant. ANOVA followed by *post hoc analysis* with the Dunnett's multiple comparison test was used.

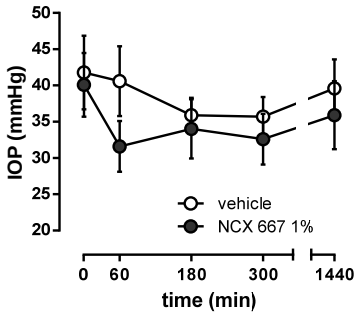
RESULTS

NCX 667 lowers IOP in ocular normotensive NZW rabbits



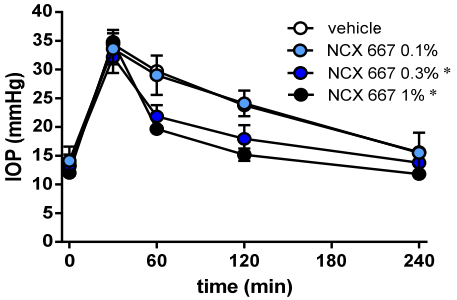
Data are reported as mean ± SEM of n= 6
*p<0.05 vs vehicle.

NCX 667 lowers IOP in ocular hypertensive non-human primates



Data are reported as mean ± SEM of n= 6

NCX 667 lowers IOP in ocular hypertensive NZW rabbits



Data are reported as mean ± SEM of n= 8
*p<0.05 vs vehicle.

NCX 667, timolol and travoprost IOP lowering effects in rabbits and non-human primates

	Normotensive rabbits	Hypertensive rabbits	Hypertensive non-human primates
compound	E_{max} (mmHg)	E_{max} (mmHg)	E_{max} (mmHg)
NCX 667 1%	-5.3 ± 0.8*#	-9.0 ± 0.6*	-7.3 ± 2.3
timolol 1%	-0.9 ± 0.4	-8.4 ± 1.2	-7.7 ± 1.0
travoprost 0.03%	-0.7 ± 0.5	-3.5 ± 0.9	-7.0 ± 4.3

E_{max} = $(IOP_{drug} - IOP_{pre\ dose\ drug}) - (IOP_{veh} - IOP_{pre\text{-}dose\ veh})$ where changes are maximal ± SEM. NCX 667 and timolol were dissolved in the same vehicle as described in the methods section. Travoprost was prepared using buffered aqueous solution pH 6, polyoxyl 40 hydrogenated castor oil 5mg/ml, tromethamine 10mg/ml, boric acid 6mg/ml, mannitol 40mg/ml, edetate disodium 0.5mg/ml and belzalkonium chloride 0.15mg/ml.
*p<0.05 vs travoprost; #p<0.05 vs timolol

NCX 667 might represent a valid alternative to current IOP-lowering treatments

SUMMARY

- **NCX 667 reduces IOP up to 5.3±0.8 mmHg in ocular normotensive NZW rabbits.**
- **Maximal IOP reduction of 9.0±0.6 mmHg in ocular hypertensive NZW rabbits.**
- **IOP lowering effects are dose-dependent from 0.1 to 1% in ocular normotensive and hypertensive NZW rabbits.**
- **NCX 667 is effective (-7.3 ± 2.3 mmHg) in the ocular hypertensive eyes of non-human primates.**
- **NCX 667 is safe and well tolerated following single topical dosing in rabbits and non-human primates.***

REFERENCES

1. Toda N, Nakanishi-Toda M. Nitric oxide: ocular blood flow, glaucoma, and diabetic retinopathy. *Prog Retin Eye Res*. 2007; 26:205-238.
2. Cavet M, Vittitow JL, Impagnatiello F, Ongini E, Bastia E. Nitric Oxide (NO): An emerging target for the treatment of glaucoma. *Invest Ophthalmol Vis Sci*. 2014; 55:5005-5015.
3. Galassi F, Renieri G, Sodi A, Ucci F, Vannozzi L, Masini E. Nitric oxide proxies and ocular perfusion pressure in primary open angle glaucoma. *Br J Ophthalmol*. 2004; 88:757-760.
4. Buys E, Ko YC, Alt C, et al., Soluble guanylate cyclase alpha 1-deficient mice: a novel murine model of primary open angle glaucoma. *PLoS One*. 2013; 8(3):e60156.
5. Nathanson, JA. Nitrovasodilators as a new class of ocular hypotensive agents. *J Pharmacol Exp Ther*. 1992; 260:956-965.
6. Heyne GW, Kiland JA, Kaufman PL, Gabelt BT. Effect of nitric oxide on anterior segment physiology in monkeys. *Invest Ophthalmol Vis Sci*. 2013; 54:5103-5110.
7. Chuman H, Chuman T, Nao-I N, Sawada A. The effect of L-arginine on intraocular pressure in the human eye. *Curr Eye Res*. 2000;20:511-516.
8. Wizemann AJ, Wizemann V. Organic nitrate therapy in glaucoma. *Am J Ophthalmol*. 1980;90:106-109.
9. Weinreb RN, Ong T, Scassellati Sforzolini B, Vittitow JL, Singh K, Kaufman PL for the VOYAGER study group. 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*. 2014; Epub ahead of print.

* Data not shown

Commercial Relationships Disclosure:

E. Bastia, Nicox Research Institute (E), F. Impagnatiello, Nicox Research Institute (C), N. Almirante, Nicox Research Institute (E), C. Lanzi, Nicox Research Institute (F), E. Masini, Nicox Research Institute (F), C. Toris, Nicox Research Institute (F), E. Ongini, Nicox Research Institute (C).

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