IOP-lowering effects of NCX 667 in combination with travoprost in ocular normotensive and transient hypertensive rabbits

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INTRODUCTION

Nitric oxide (NO) and prostaglandin F2alpha (PGF2α) analogues lower intraocular pressure (IOP) by increasing aqueous humor outflow via relaxation of the trabecular meshwork and Schlemm's canal (conventional route) and through the uveoscleral pathway (nonconventional route), respectively.[1-2] Both mechanisms have been combined into Latanoprostene bunod, a novel NO-donating prostanoid FP receptor agonist, proven to be safe and effective in lowering IOP in adults with glaucoma or ocular hypertension.[3-5] NCX 667 is a novel stand alone NO-donor, potentially useful for treating ocular hypertension and glaucoma alone or combined with standard-of-care treatments.

METHODS

Ocular transient 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), travoprost (0.004%, Travatan®) or NCX 667 was instilled immediately before saline injection. Two treatment paradigms were followed: A, NCX 667 was administered 10 min before travoprost; B, NCX 667 was dosed 10 min after travoprost. IOP was determined using a Tono-pen AVIA (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.

Ocular normotensive rabbits

Treatment paradigms A and B were used as described above. IOP recording was determined prior to (baseline) and during the following 5 hours post dosing using a pneumatonometer (Model 30™ Reichert, Depew, NY, USA).

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 Tukey's multiple comparison test was used.

NCX 667 dose-dependently lowers IOP in transient ocular hypertensive and normotensive rabbits

	Normotensive rabbits	Hypertensive rabbits
NCX 667 (%)	E_{max} (mmHg)	E_{max} (mmHg)
0.1	-2.7 ± 0.4*	-0.4 ± 1.1
0.3	-4.6 ± 1.0*	-7.7 ± 0.5*
1.0	-5.3 ± 0.8*	-11.8 ± 0.6*

E_{max} = $(IOP_{drug} - IOP_{pre\ dose\ drug}) - (IOP_{veh} - IOP_{pre\text{-}dose\ veh})$ where changes are maximal ± SEM (n=6-8).
* p<0.05 vs vehicle

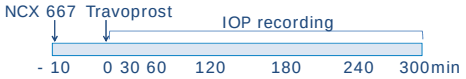
PURPOSE

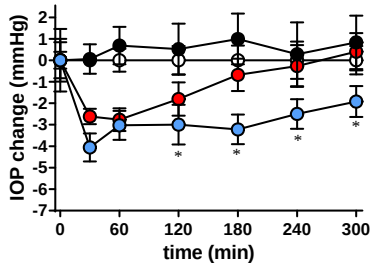
To study NCX 667, a novel NO donor, for IOP lowering efficacy alone and combined with clinically relevant doses of travoprost in New Zealand white rabbits

RESULTS

NCX 667 combined with travoprost results in superior efficacy and duration vs. each drug given alone in ocular normotensive NZW rabbits

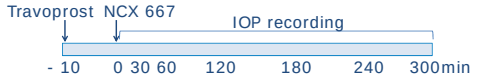
Treatment paradigm A

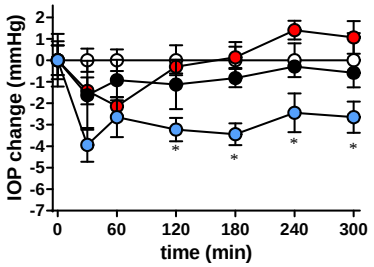




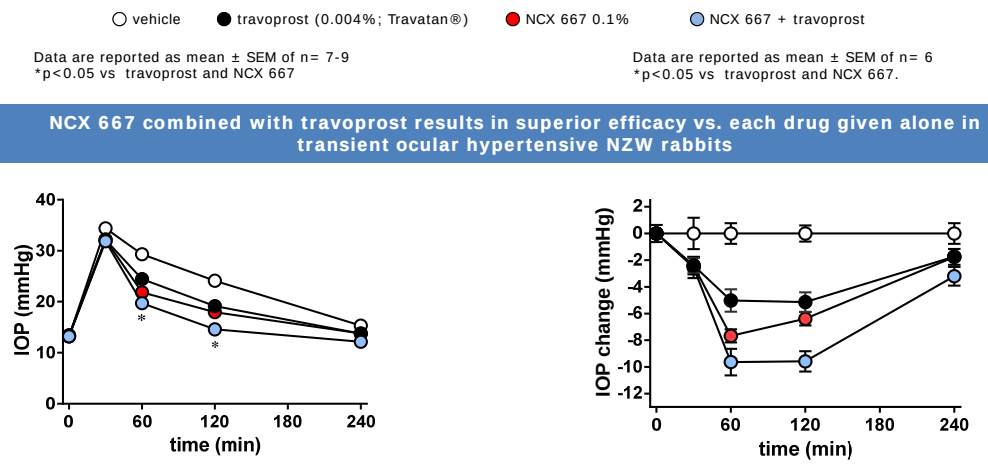
Data are reported as mean ± SEM of n= 7-9
*p<0.05 vs travoprost and NCX 667

Treatment paradigm B





Data are reported as mean ± SEM of n= 6
*p<0.05 vs travoprost and NCX 667.



NCX 667 combined with travoprost results in superior efficacy vs. each drug given alone in transient ocular hypertensive NZW rabbits

Figure refers to treatment paradigm B. IOP change was calculated as follows: (Drug IOPTx-Drug IOPT0) - (Veh IOPTx - Veh IOPT0) where IOPTx and IOPT0 are respectively the IOP at the time of interest and prior to dosing. Data are reported as mean ± SEM of n= 14-22; *p<0.05. Treatment paradigm A resulted in similar data.

SUMMARY

- **NCX 667 shows dose-dependent IOP lowering in two rabbit models.**
- **Travoprost (0.004%) is poorly effective in ocular normotensive and hypertensive rabbits.**
- **NCX 667 dosed either before or after travoprost results in superior efficacy and duration vs. each drug given alone in ocular normotensive and hypertensive rabbits.**
- **NCX 667 is safe and well tolerated alone and in combination with travoprost following single topical dosing in rabbits seen by visual inspection (data not shown).**

CONCLUSION

NCX 667 IOP-lowering activity is strengthened and prolonged when combined with the PGF2α agonist travoprost

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