

# NCX 1741, a novel NO-donating derivative of the phosphodiesterase-5 inhibitor avanafil, reduces IOP in models of ocular hypertension and glaucoma

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## INTRODUCTION

The nitric oxide (NO)/cyclic guanosine monophosphate (cGMP) signaling pathway plays a major role in aqueous humour drainage and intraocular pressure (IOP) homeostasis<sup>1,2</sup>. The effects of this signaling pathway are silenced when cGMP is degraded by the phosphodiesterase type-5 enzyme (PDE5)<sup>3</sup>. NCX 1741, a NO-donating derivative of avanafil (avanafil is a US- and EU-approved second-generation PDE5 inhibitor for the treatment of erectile dysfunction), is a new molecular entity holding two modes of actions (MoAs), namely PDE5 enzyme inhibition and NO/soluble guanylyl cyclase signaling activation that could co-operate to effectively lower IOP in patients with ocular hypertension and glaucoma. Specifically, here we report on the initial pharmacological characterization of NCX 1741 in animal models of glaucoma and ocular hypertension.

## METHODS

### Intraocular pressure (IOP) studies

Ocular normotensive New Zealand White rabbits (ONT-rabbits, n=8) and monocular laser-induced ocular hypertensive cynomolgus monkeys (OHT-monkeys, n=8) were used. NCX 1741 or the respective vehicle (phosphate buffer pH 6.0, Cremophor EL 5%, DMSO 0.3%, BAC 0.02%), were instilled (30 µL) in a masked fashion and IOP was measured by pneumatonometry prior to (baseline) and periodically post-dosing for 5h (ONT-rabbits) or 24h (OHT-monkeys).

### Aqueous humor (AH) exposure studies

Aqueous humor (AH) content of NCX 1741 and its main metabolite, avanafil were followed. Male New Zealand white rabbits weighing 1.8-2.0 kg were used. All animals received a single 30 µL topical dose of NCX 1741 dissolved in phosphate buffer pH 6.0, Cremophor EL 5%, DMSO 0.3%, BAC 0.02%. Animals were euthanized at the indicated time-points and the aqueous humor (AH) collected (about 100 µL) and chill frozen until further processing. On the day of the analysis, the samples were thawed, protein precipitated using acetonitrile, centrifuged and the supernatant collected for LC-MS/MS analysis.

### Commercial Relationships Disclosure:

F. Impagnatiello, E. Bastia, S. Brambilla, C. Galli and N. Almirante, Nicox Research Institute (E); T. Navratil, Nicox Ophthalmics, Inc. (E); M.V.W. Bergamini, Nicox S.A. (C); S. Fan, University of Nebraska Medical Center, Omaha, Nebraska, (None); C. Toris, Case Western Reserve University, Cleveland (F)

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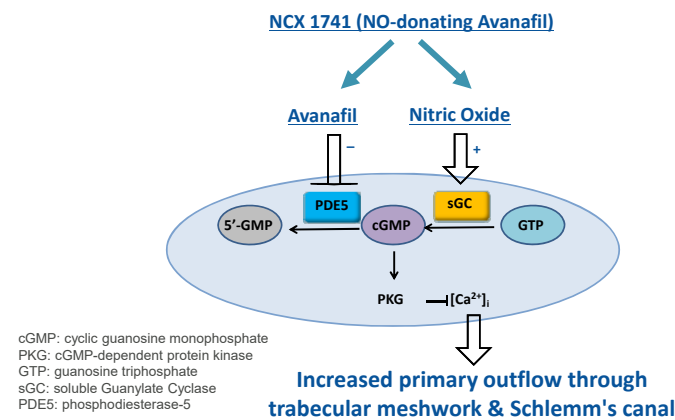
## PURPOSE

Address the IOP-lowering effects of NCX 1741, a novel NO-donating derivative of the PDE5 inhibitor avanafil in rabbit and non-human primate models of ocular hypertension and glaucoma

## RESULTS

### IOP-lowering and aqueous humor (AH) exposure in ocular normotensive rabbits (ONT-rabbits)

#### Schematic representation of NO and PDE5 signaling cascade

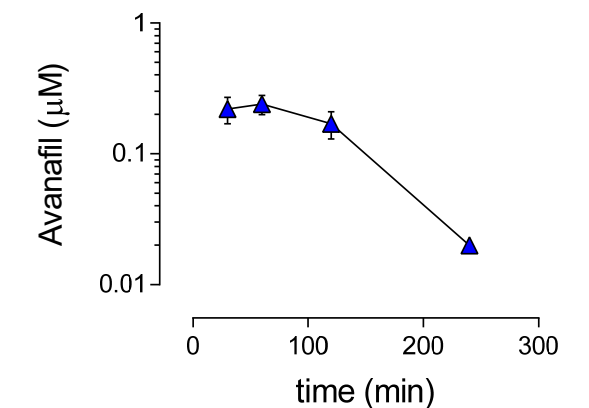


#### NCX 1741-mediated IOP-lowering in ONT-rabbits

Model	ONT-rabbits
Dose (%)	2.2
E <sub>max</sub> (IOP-change, mmHg)	- 2.8 ± 0.5
T <sub>max</sub> (min)	60

IOP-change = (Drug IOP<sub>Tx</sub> - Drug IOP<sub>T0</sub>) - (Veh IOP<sub>Tx</sub> - Veh IOP<sub>T0</sub>) where IOP<sub>Tx</sub> and IOP<sub>T0</sub> are respectively the IOP at the time of interest and prior to dosing

#### Aqueous humor (AH) avanafil content in NCX 1741-treated ONT-rabbits



## CONCLUSIONS

- Avanafil is found in AH of ONT-rabbits following NCX 1741 ocular dosing
- NCX 1741 safely and effectively lowers IOP in ONT-rabbits and OHT-monkeys
- In OHT-monkeys, the IOP-lowering effects of NCX 1741 appear to last up to 24 hours

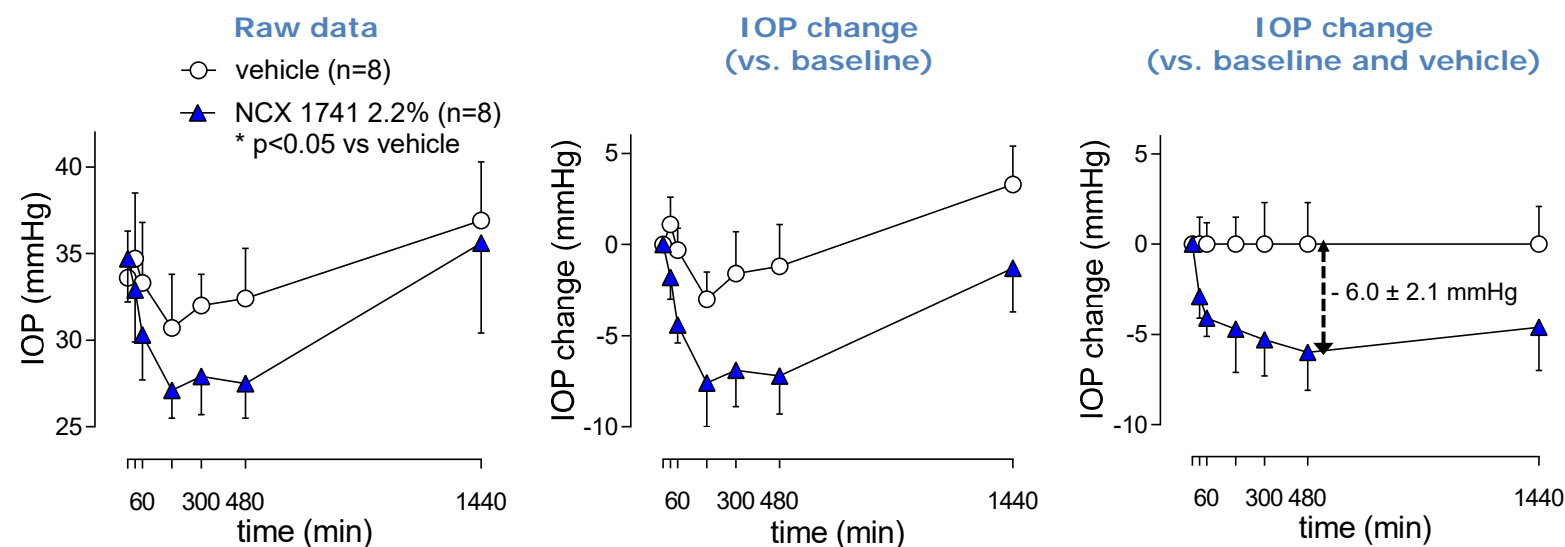
**NCX 1741 may represent a new and effective IOP-lowering agent to treat ocular hypertension and glaucoma**

## REFERENCES

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### IOP-lowering in ocular hypertensive cynomolgus monkeys (OHT-monkeys)



\* p<0.05 vs. Vehicle, two-tailed t-tests