

# **AQUEOUS HUMOR DYNAMICS OF NCX 470 OPHTHALMIC SOLUTION (NITRIC OXIDE-DONATING BIMATOPROST):**

**A DOUBLE-MASKED, PLACEBO-CONTROLLED, PHASE 3B CLINICAL TRIAL**

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# DISCLOSURES

**This study sponsored by Nicox Ophthalmics, Inc.**

Aerie Pharmaceuticals Inc. (C, S)

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National Eye Institute



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Foundation**

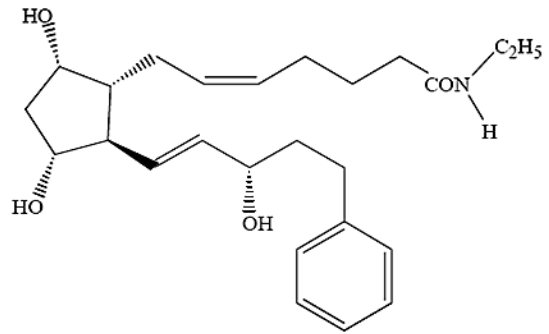
Cure in Mind. Cure in Sight.



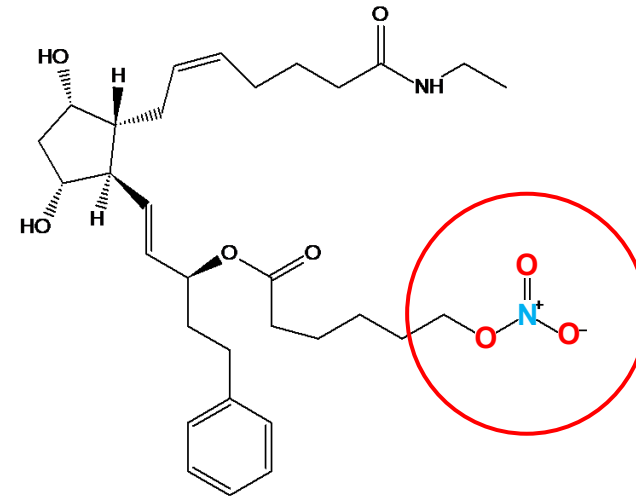
**AMERICAN  
GLAUCOMA  
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# NCX 470

Bimatoprost



Nitric oxide (NO)-donating bimatoprost



MONT BLANC Study<sup>2</sup>: “NCX 470 0.1% was well-tolerated and lowered IOP more than latanoprost in subjects with OAG or OHT”

## What is the mechanism of action in human eyes?

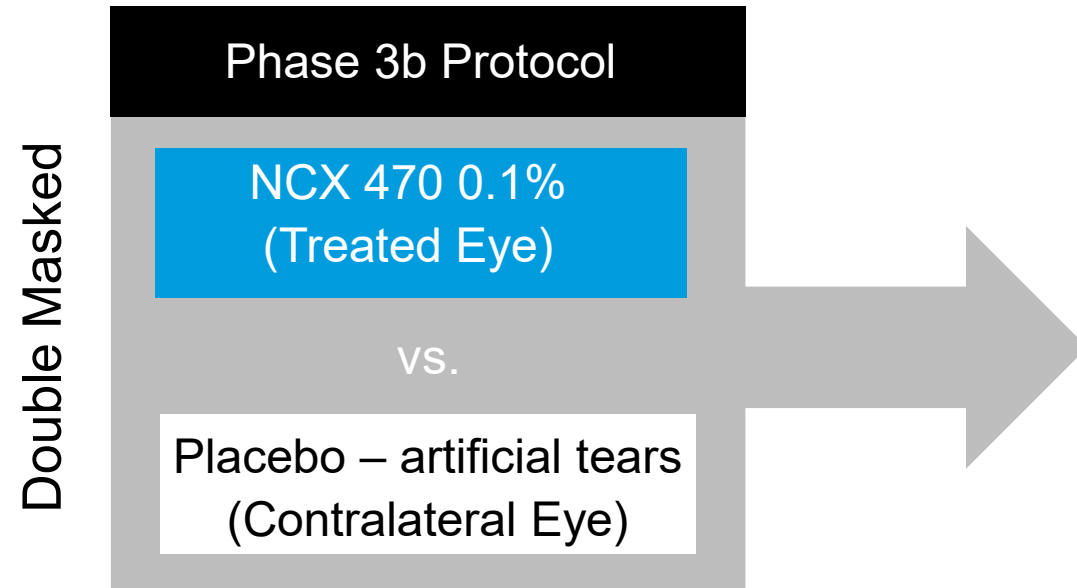
1. Impagnatiello F et al. NCX 470, a nitric oxide (NO)-donating prostaglandin analog, restores ocular hemodynamic and photoreceptor function after endothelin-1-induced ischemia/reperfusion injury in rabbits. *Invest Ophthalmol Vis Sci* 2022; 63(7):1606 – A0429.

2. Fechtner R, et al. A Randomized, Controlled Comparison of NCX 470, a Nitric Oxide-Donating Bimatoprost, and Latanoprost in Subjects with Open-Angle Glaucoma or Ocular Hypertension: The MONT BLANC Study. *Am J Ophthalmol*. 2024 Aug;264:66-74.

# METHODS – STUDY DESIGN AND OBJECTIVES

**OBJECTIVE:** To evaluate the effects of NCX 70 on aqueous humor dynamics (AHD) parameters

## DESIGN:



## PROTOCOL:

Diurnal (1 PM and 3 PM)\* AHD measures on Day 1 vs Day 8:

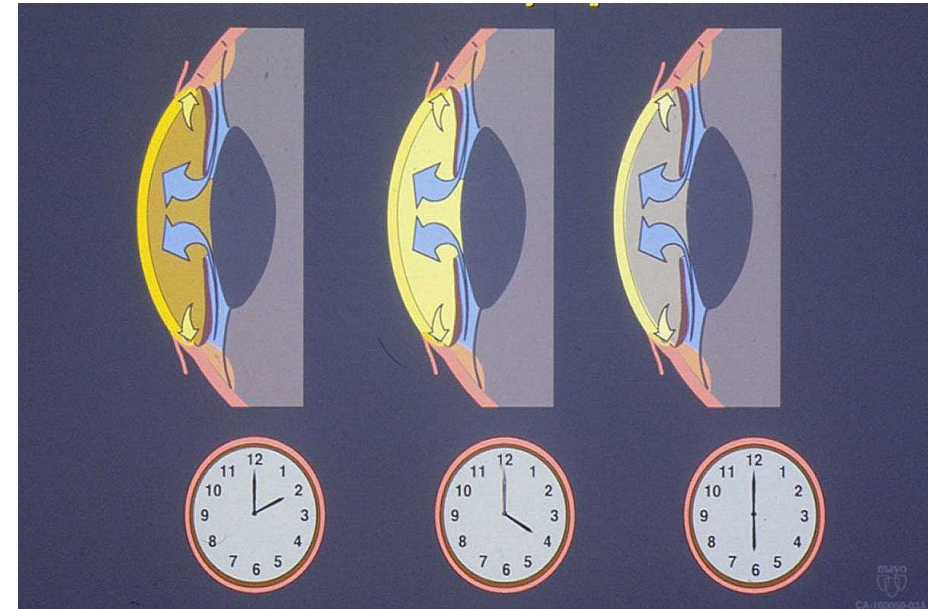
- IOP
- Outflow facility
- EVP
- Aqueous humor production (measured once)\*
- Uveoscleral outflow rate (calculated)

**SUBJECTS:** Healthy adults with or without OHT (none on treatment)

# AQUEOUS FLOW RATE BY FLUOROPHOTOMETRY



Scanning ocular fluorophotometer

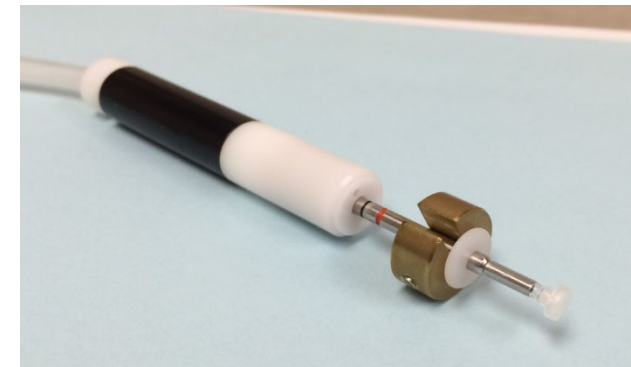
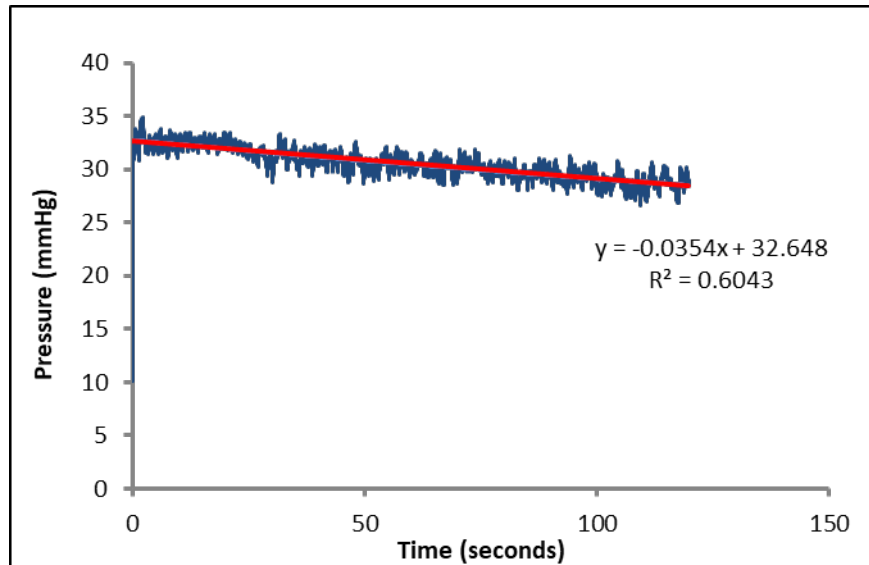


Fluorescein is diluted by aqueous humor

Aqueous humor flow rate determined from rate of fluorescein clearance

# OUTFLOW FACILITY BY PNEUMATONOGRAPHY

IOP decay curve from constant-weight tonography:



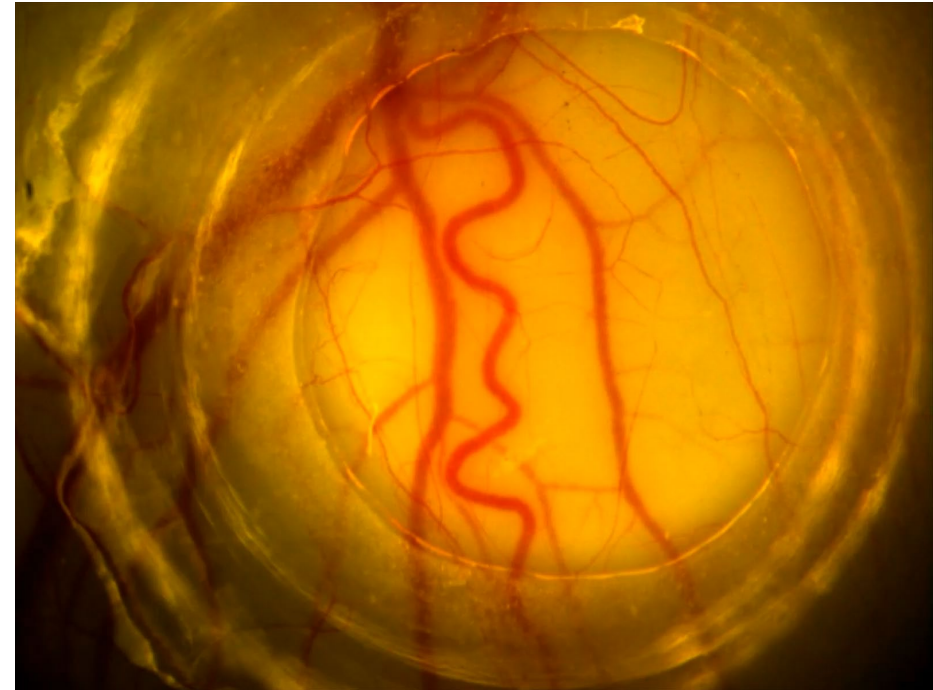
Facility calculated from Friedenwald equation:

$$C = \frac{\Delta V / \Delta t}{\Delta P}$$

Kazemi A, McLaren JW, Lin SC, Toris CB, Gulati V, Moroi SE, Sit AJ. Comparison of Aqueous Outflow Facility Measurement by Pneumatography and Digital Schiøtz Tonography. Invest Ophthalmol Vis Sci. 2017 Jan 1;58(1):204-210.

# EVP BY OBJECTIVE VENOMANOMETRY

Episcleral vein compression



25X magnification

EVP determined from pressure to begin vein collapse

Sit AJ, Ekdawi NS, Malihi M, McLaren JW. A novel method for computerized measurement of episcleral venous pressure in humans. *Exp Eye Res.* 2011 Jun;92(6):537-44.

Sit AJ, McLaren JW. Measurement of episcleral venous pressure. *Exp Eye Res.* 2011 Sep;93(3):291-8.

# UVEOSCLERAL OUTFLOW RATE CALCULATION

- Calculated from modified Goldmann equation

$$U = Q - c(IOP - EVP)$$

Where:

$Q$  = aqueous outflow rate

$U$  = uveoscleral outflow rate

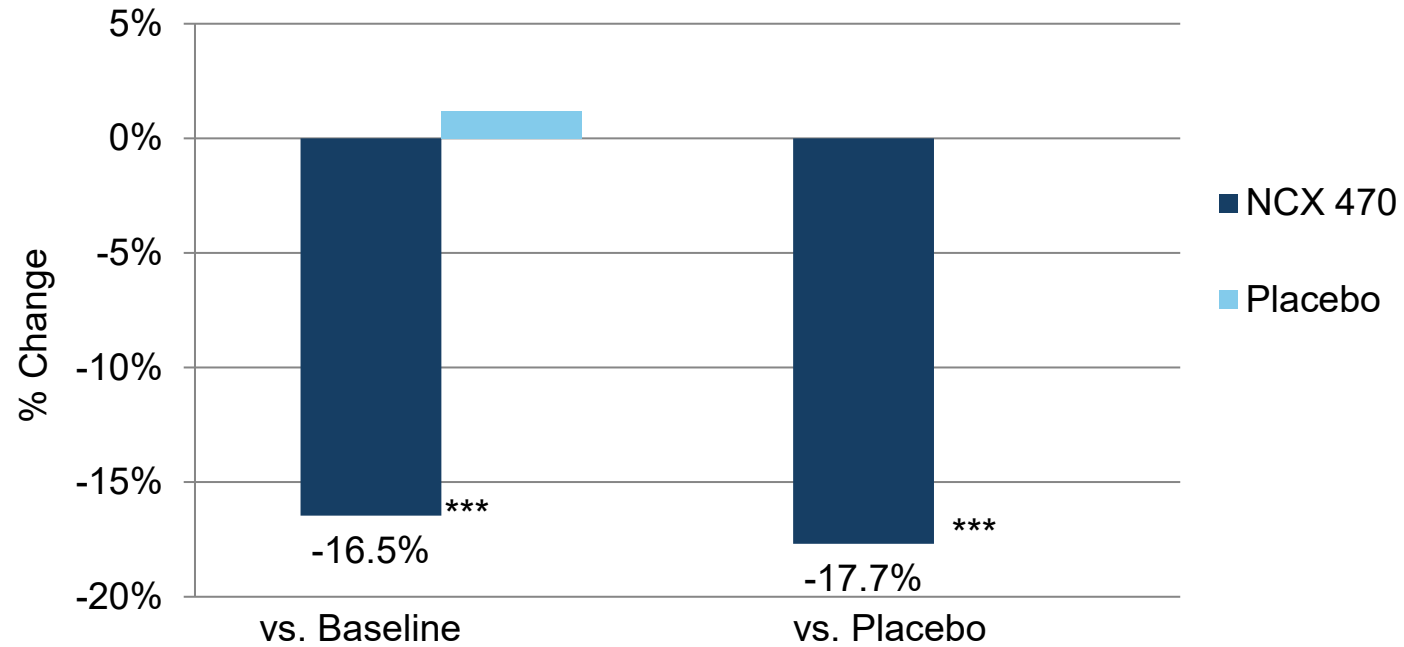
$c$  = outflow facility

$P_e$  = episcleral venous pressure

# BASELINE DEMOGRAPHICS

- N = 18
- 4 OHT at screening
- 13 female, 5 male
- Age  $45.6 \pm 17.3$  yrs
- 94.4% White

# EFFECT ON IOP



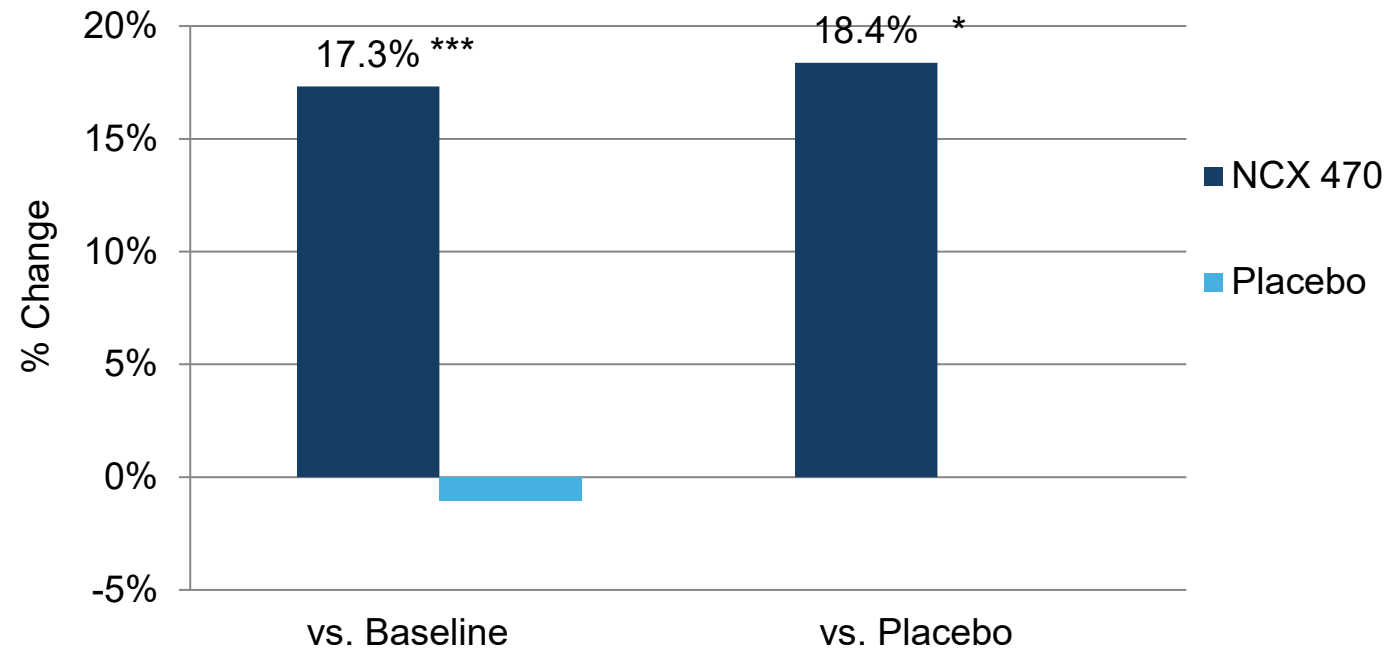
\*\*\* p<0.001

\* p<0.05

N = 18

Mean Diurnal IOP (mmHg)	NCX 470	Placebo
<b>Baseline</b>	16.4 ± 2.9	16.6 ± 2.5
<b>Day 8</b>	13.6 ± 1.8	16.8 ± 2.3
<b>Change from baseline</b>	-2.7 ± 1.3	0.2 ± 0.9
<b>P</b>	<0.001	0.381

# EFFECT ON OUTFLOW FACILITY



\*\*\* p<0.001

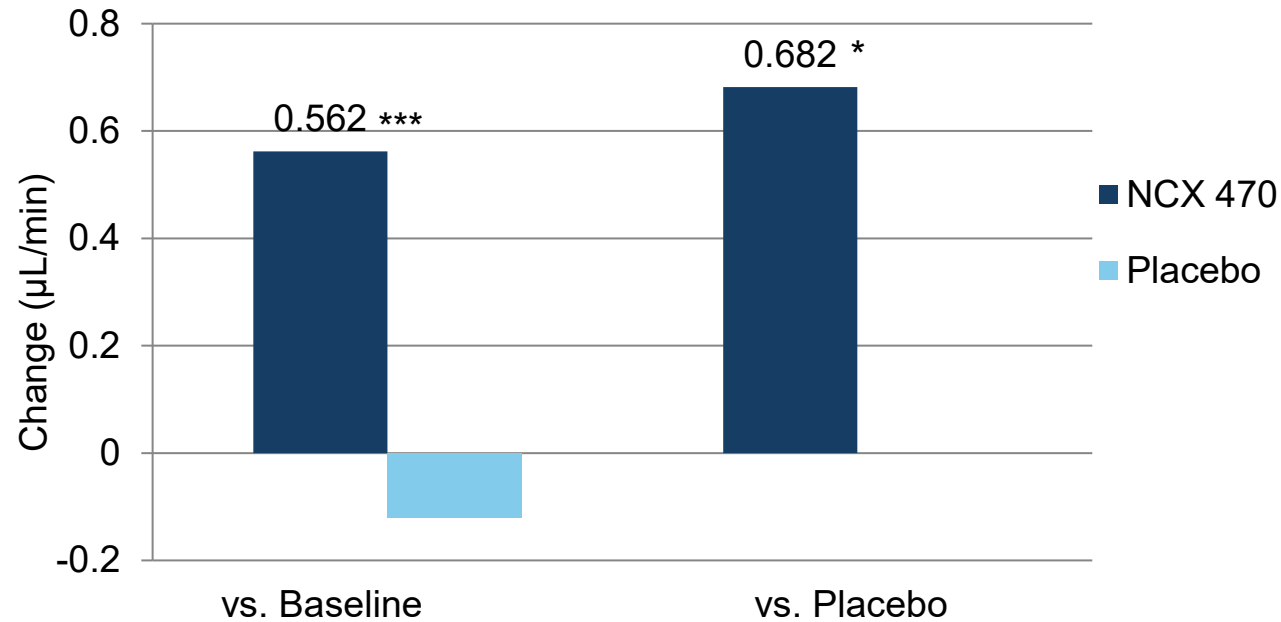
\* p<0.05

N = 18

Mean Diurnal Facility ( $\mu\text{L}/\text{min}/\text{mmHg}$ )	NCX 470	Placebo
<b>Baseline</b>	0.283 $\pm$ 0.074	0.293 $\pm$ 0.077
<b>Day 8</b>	0.332 $\pm$ 0.087	0.291 $\pm$ 0.093
<b>Change from baseline</b>	0.049 $\pm$ 0.043	-0.003 $\pm$ 0.078
<b>P</b>	<0.001	0.881

Outflow facility increase accounted for 42% of observed IOP reduction

# EFFECT ON UVEOSCLERAL OUTFLOW RATE



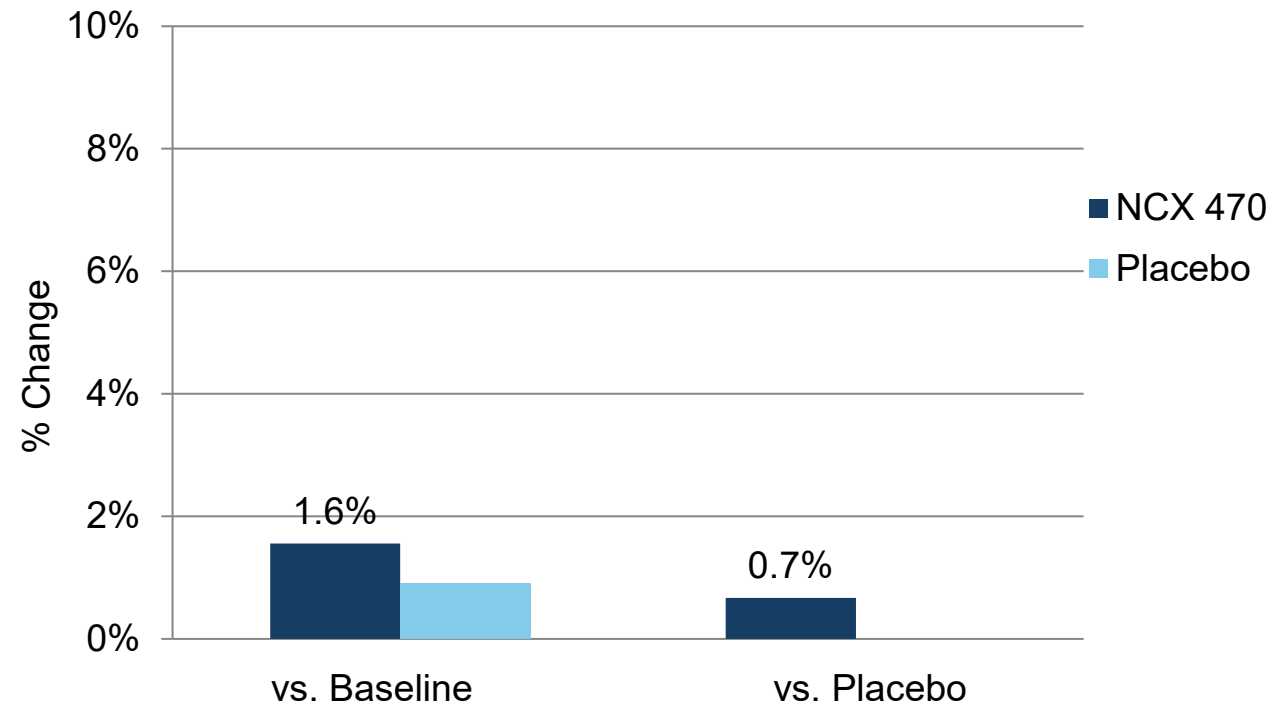
\*\*\* p<0.001  
\* p<0.05

N = 18

Mean Diurnal Uveoscleral Outflow (µL/min)	NCX 470	Placebo
<b>Baseline</b>	-0.12 ± 0.83	-0.41 ± 1.01
<b>Day 8</b>	0.44 ± 0.80	-0.53 ± 1.25
<b>Change from baseline</b>	0.56 ± 0.45	-0.12 ± 0.86
<b>P</b>	<0.001	0.558

Uveoscleral flow increase accounted for 58% of observed IOP reduction

# EFFECT ON EVP



\*\*\* p<0.001  
\* p<0.05

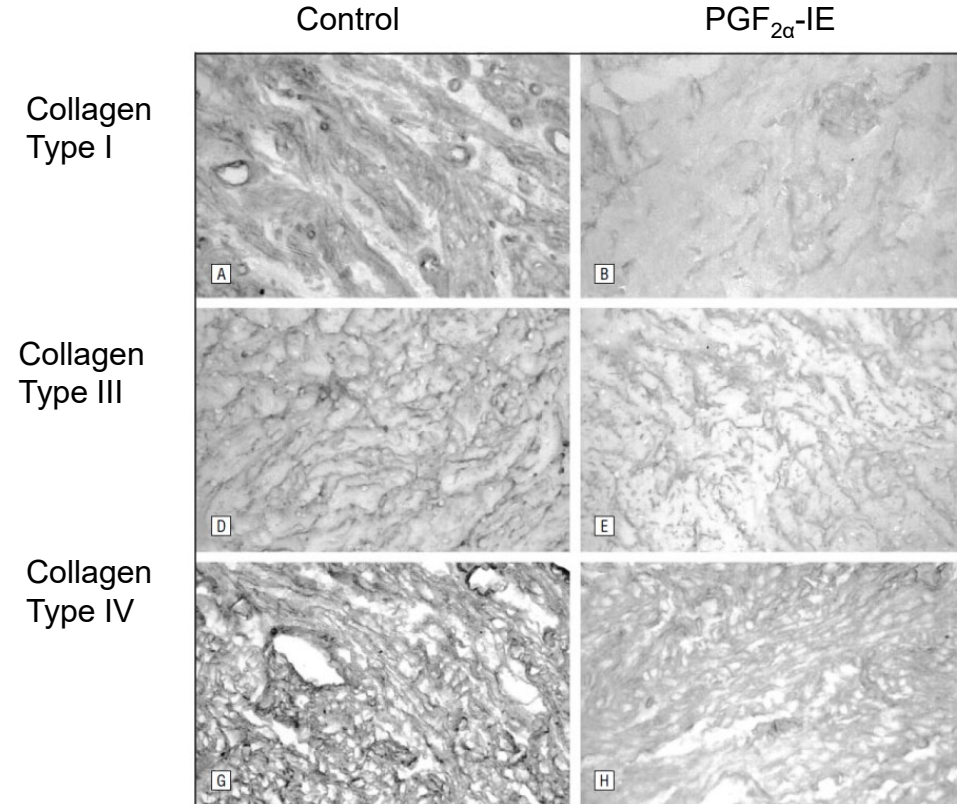
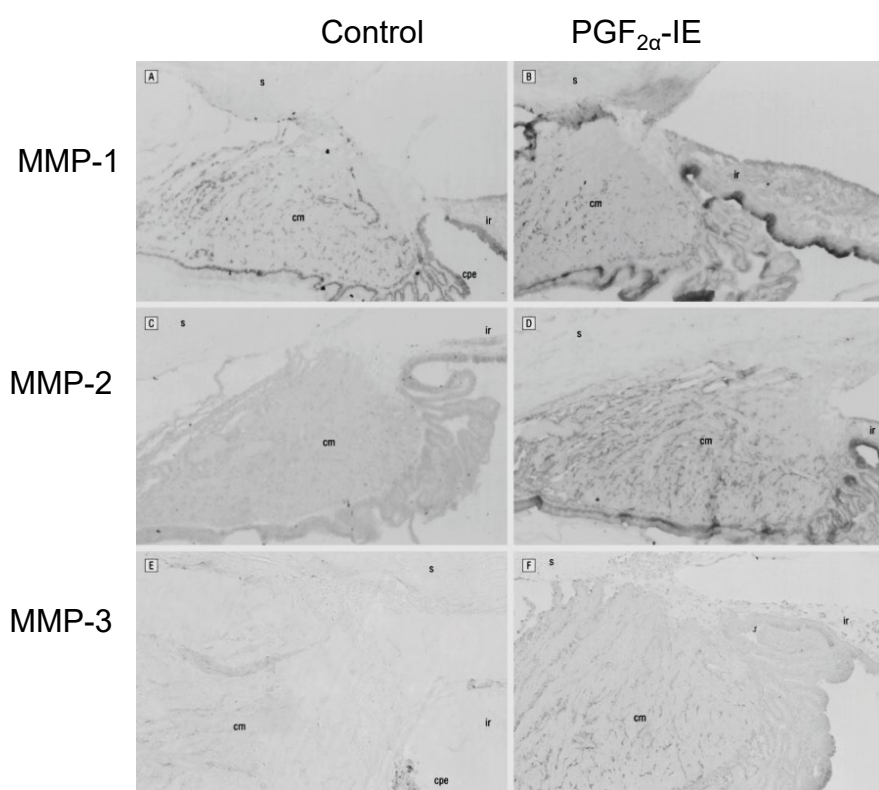
N = 18

Mean Diurnal EVP (mmHg)	NCX 470	Placebo
<b>Baseline</b>	6.56 ± 1.18	6.29 ± 0.79
<b>Day 8</b>	6.66 ± 1.11	6.34 ± 0.92
<b>Change from baseline</b>	0.10 ± 0.43	0.06 ± 0.22
<b>P</b>	0.329	0.288

# ADVERSE EVENT SUMMARY

	NCX 470 0.1% (N = 18)	Placebo (N = 18)
<b>Eye Disorders</b>		
Ocular hyperemia	6 (33.3%)	1 (5.6%)
Conjunctival hyperemia	5 (27.8%)	0
Dry eye	5 (27.8%)	1 (5.6%)
Eye irritation	3 (16.7%)	1 (5.6%)
Eye pruritus	2 (11.1%)	0
Photophobia	2 (11.1%)	0
Eye pain	1 (5.6%)	0
Swelling of eyelid	1 (5.6%)	1 (5.6%)
<b>General Disorders and Administration Site Conditions</b>		
Instillation site erythema	2 (11.1%)	0
Instillation site pain	2 (11.1%)	0
<b>Nervous System Disorders</b>		
Headache	3 (16.7)	3 (16.7)

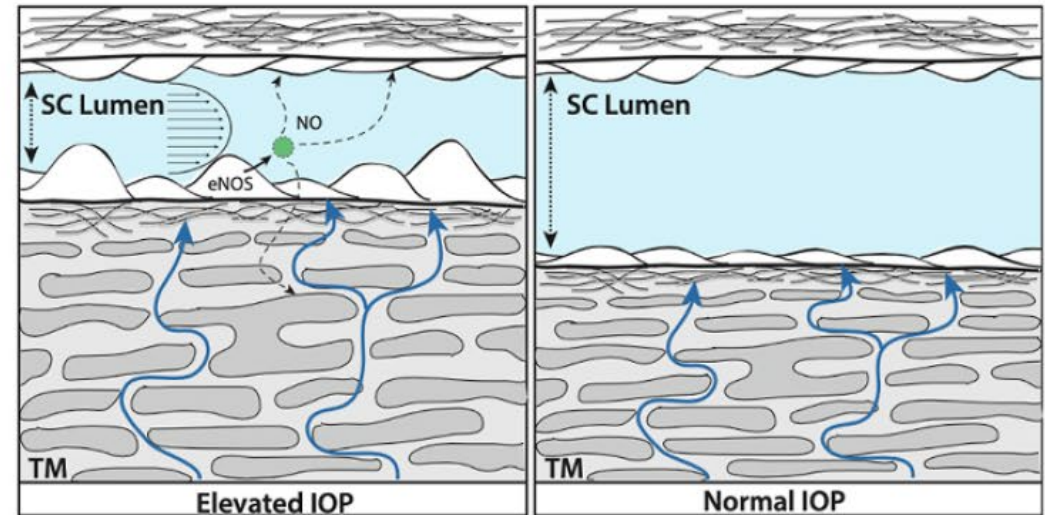
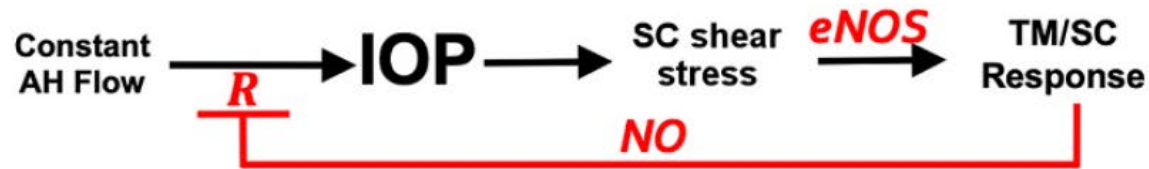
# DISCUSSION – UVEOSCLERAL OUTFLOW



PGs increase MMPs and reduce collagen type I, III, and IV in the ciliary body, iris root and sclera

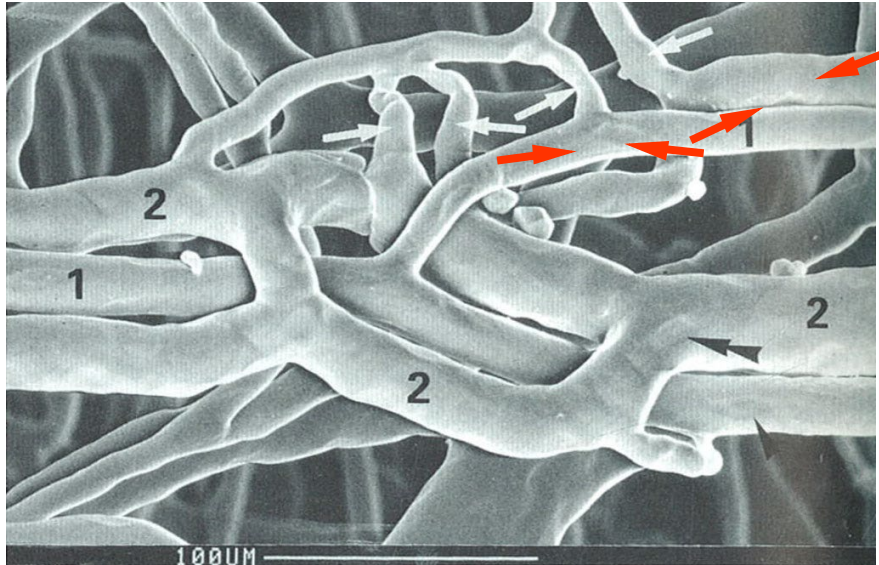
1. Gatton DD et al. Increased matrix metalloproteinases 1, 2, and 3 in the monkey uveoscleral outflow pathway after topical prostaglandin F(2 alpha)-isopropyl ester treatment. Arch Ophthalmol. 2001 Aug;119(8):1165-70.
2. Sagara T et al. Topical prostaglandin F2alpha treatment reduces collagen types I, III, and IV in the monkey uveoscleral outflow pathway. Arch Ophthalmol. 1999 Jun;117(6):794-801.

# DISCUSSION – EFFECT OF NITRIC OXIDE ON TM



Elevated IOP causes increased endothelial shear stress, release of NO, and SC/TM relaxation

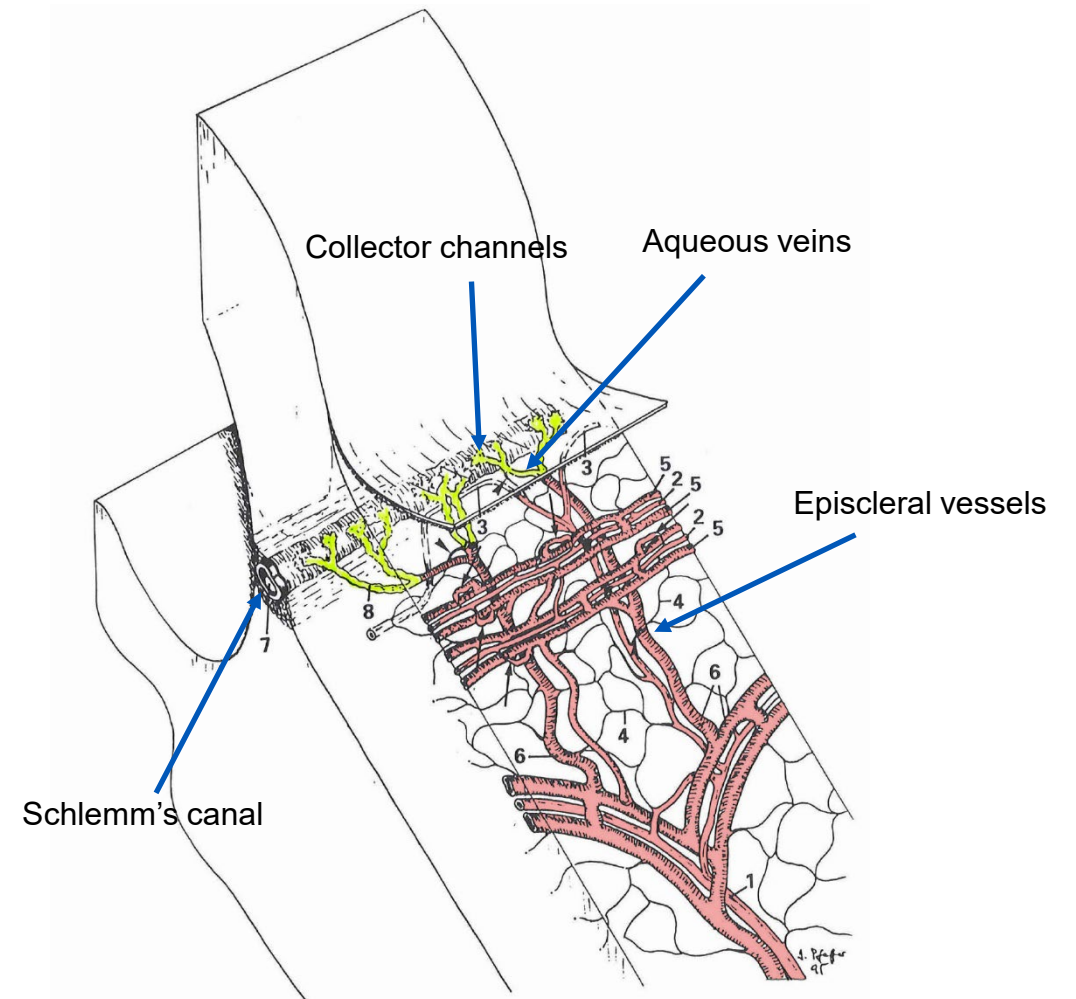
# DISCUSSION – REGULATION OF EVP



Direct connections (arteriovenous anastomoses) exist between episcleral arterioles and venules

Episcleral vein dilation can decrease EVP

AVA dilation can increase EVP



Funk RW and Rohen JW (1996). Scanning electron microscopic study of episcleral arteriovenous anastomoses in the owl and cynomolgus monkey. *Current Eye Research* 15(3): 321-7

# CONCLUSIONS

- In healthy adults without glaucoma, NCX 470 0.1% dosed once daily significantly lowered IOP by a dual mechanism of action increasing outflow facility and uveoscleral outflow



**THANK YOU!**

