Neuroprotective effect of tyrosine kinase inhibitor vorolanib in a mouse model of retinal detachment

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Purpose

VEGF-mediated posterior segment diseases are currently the leading cause of blindness in the US working population.[1] In the real world, under treatment of the wet age-related macular degeneration (wAMD) population with anti-VEGFs is believed to be a contributing factor, which has increased the need for extended durability and new mechanism of actions [2,3]

In this study, vorolanib, a pan-VEGF inhibitor, is evaluated for the additional potential to provide retinal neuroprotection, in a validated mouse model of retinal detachment.

Vorolanib, with Durasert E, is being investigated in ongoing Phase 2 trials in wAMD and diabetic retinopathy (DR), and a Phase 2 trial is planned in diabetic macular edema (DME).

1. Verana Health DR+DME Market Sizing Executive Summary. February 25 2022.

2. Sobolewska et al. *Clin Ophthalmol.* 2021;15:4317-4326.

3. Monés et al. *Ophthalmologica.* 2020;243(1):1-8.

VEGF = Vascular Endothelial Growth Factor. Durasert E = Erodible Durasert

Vorolanib provides pan-VEGFR Inhibition and potential neuroprotection

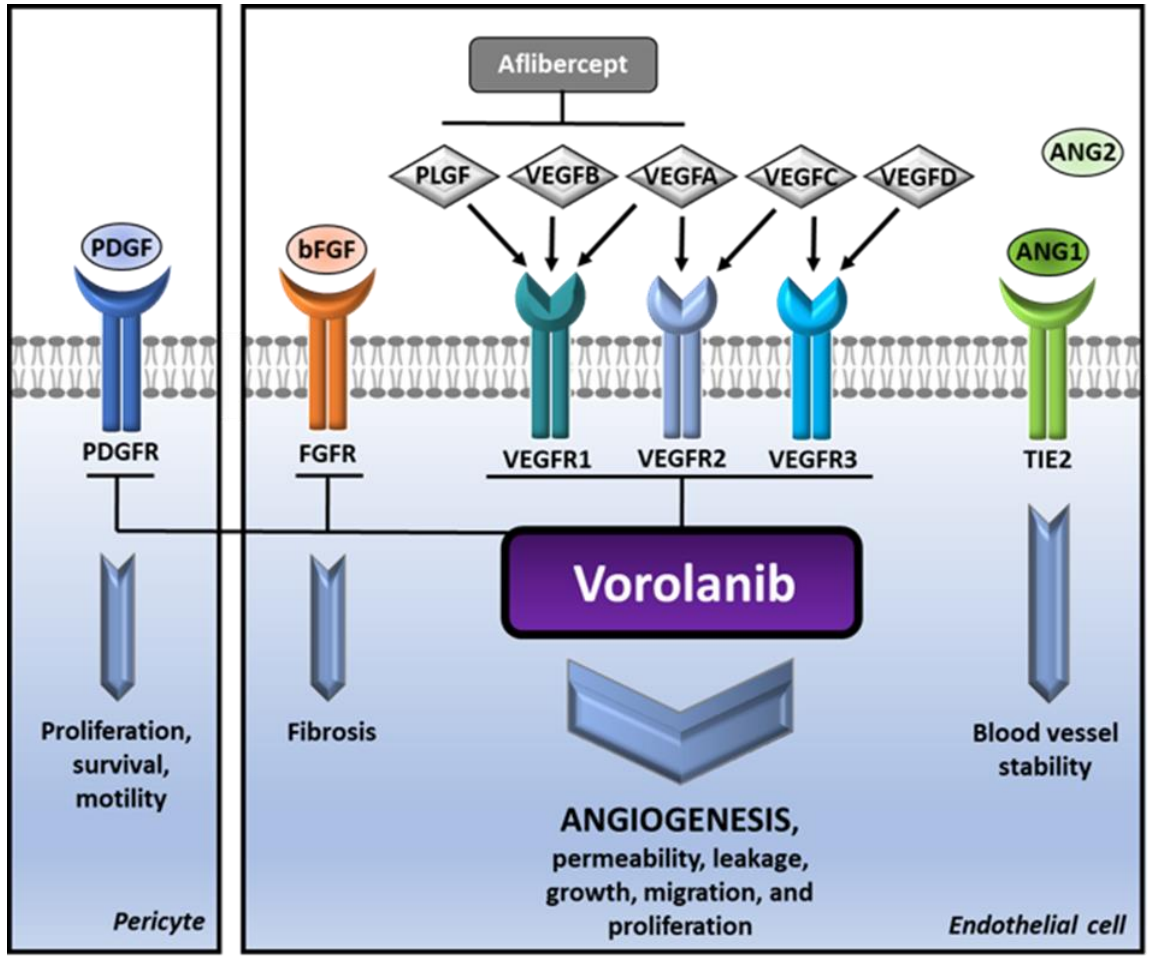
Vorolanib inhibits **multiple pathways** in the regulation of angiogenesis:

- Inhibits all **VEGFRs**
- Inhibits **PDGFRs**
- Inhibits **FGFRs**

Vorolanib inhibits pathways in the regulation of **neuronal degradation**

Vorolanib is **highly selective**

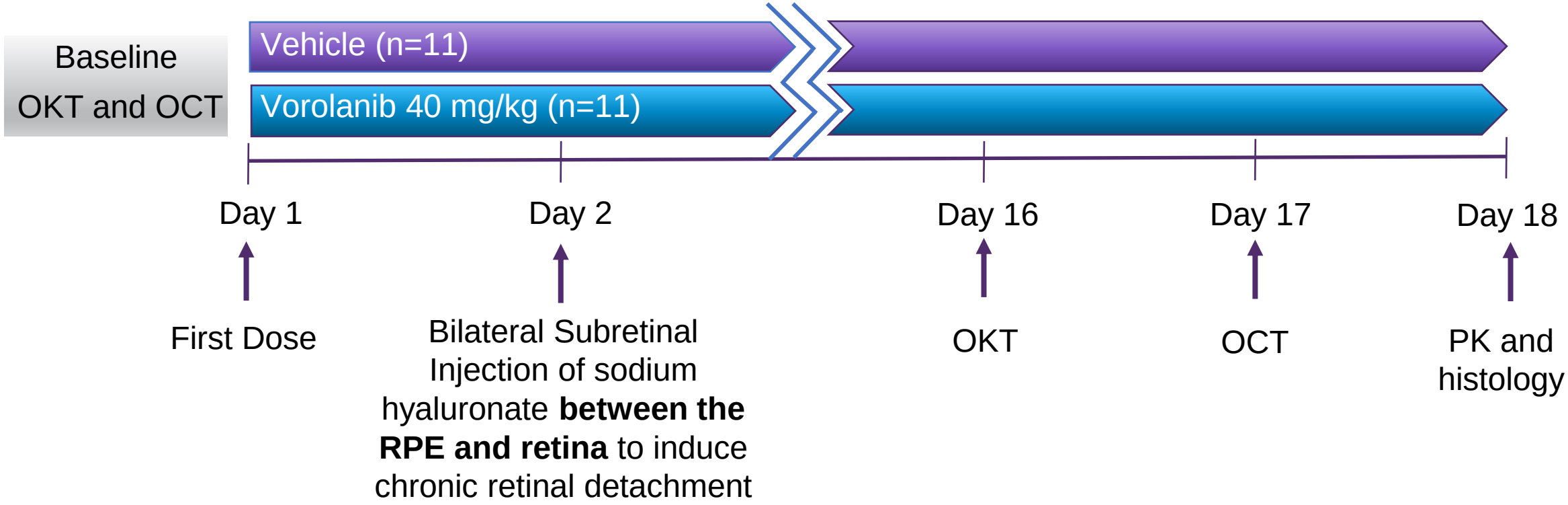
- Does not inhibit **TIE2**



VEGFR = Vascular Endothelial Growth Factor Receptor, PDGFR = Platelet Derived Growth Factors, FGFR = Fibroblast Growth Factors, DLK = Dual Leucine Zipper Kinase, JNK = c-Jun N-terminal Kinase, TIE2 = Angiopoietin-1 and 2 receptor

Study Design and Methodology

18 Day, non-GLP, daily dose study using a validated model[4] of chronic retinal detachment



Utilizes optokinetic tracking (OKT) and optical coherence tomography (OCT) to measure functional and structural changes

4. Matsumoto H, Miller JW, Vavvas DG. Journal of visualized experiments : JoVE. 2013;(79)doi: 10.3791/50660

Summary of Results

Key findings:

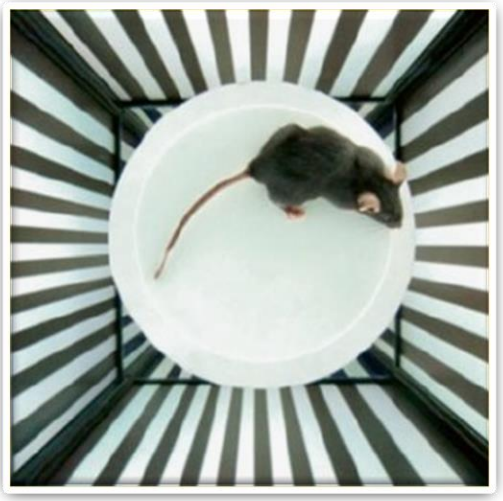
- Preclinical model reproducibly created retinal detachment in all groups
- Vorolanib demonstrated a statistically significant protective effect on contrast vision
- Vorolanib demonstrated a protective effect on ONL and visual acuity
- Vorolanib demonstrated a decrease in fibrosis and retinal atrophy
- Vorolanib reached target tissues within 30 min of dosing

Clinical Relevance:

- Vorolanib is a selective, pan-VEGFR inhibitor with a well-established mechanism of action
- Vorolanib has the potential to also protect the neuroretina, delay fibrosis and retinal atrophy
- Vorolanib as Durasert E, is under Phase 2 clinical evaluation for the treatment of VEGF-mediated retinal diseases (DAVIO2 and PAVIA)
- Durasert E is designed to consistently deliver microgram doses of vorolanib over a period of 6 month or more

Optokinetic tracking enables a reliable evaluation of contrast vision

- Established and reproducible method
- Utilizes a high contrast, rotating, visual environment
- Evaluates reflexive head and neck movements representing visual tracking
- Measures threshold for distinguishing the minimum contract between light and dark bars



Vorolanib demonstrates a statistically significant protective effect on contrast vision

34%

reduction in loss
of contrast vision vs control

Mean decrease in contrast vision	
Vehicle	**Vorolanib**
75%	41%

p value = 0.0009
(statistically significant)

The data was analyzed for significance using a 1-way ANOVA with Sidak's multiple comparison post-test for the indicated pair-wise comparison. Results are expressed as Mean and SEM.

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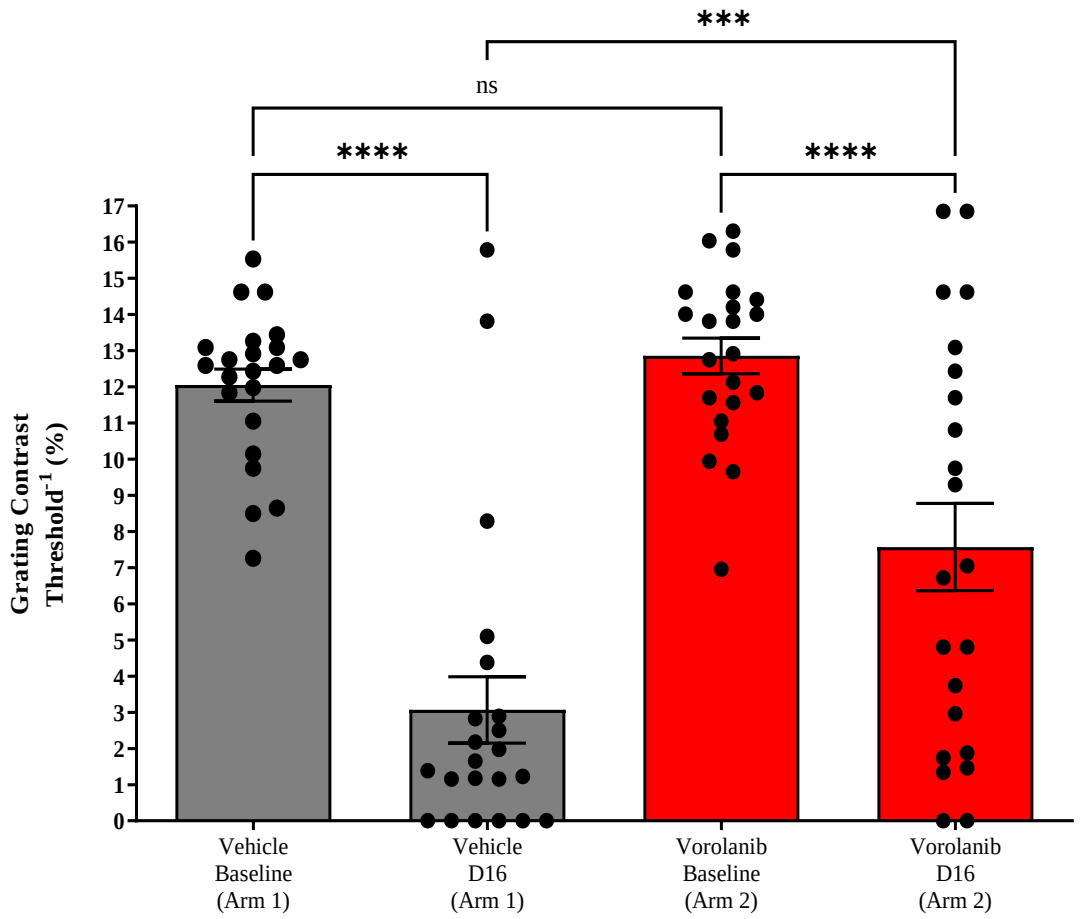
Mean Change in Contrast Vision at Day 16 from Baseline in Animals Treated with Vorolanib vs Vehicle Control



Vorolanib demonstrates a protective effect on the outer nuclear layer

<1%

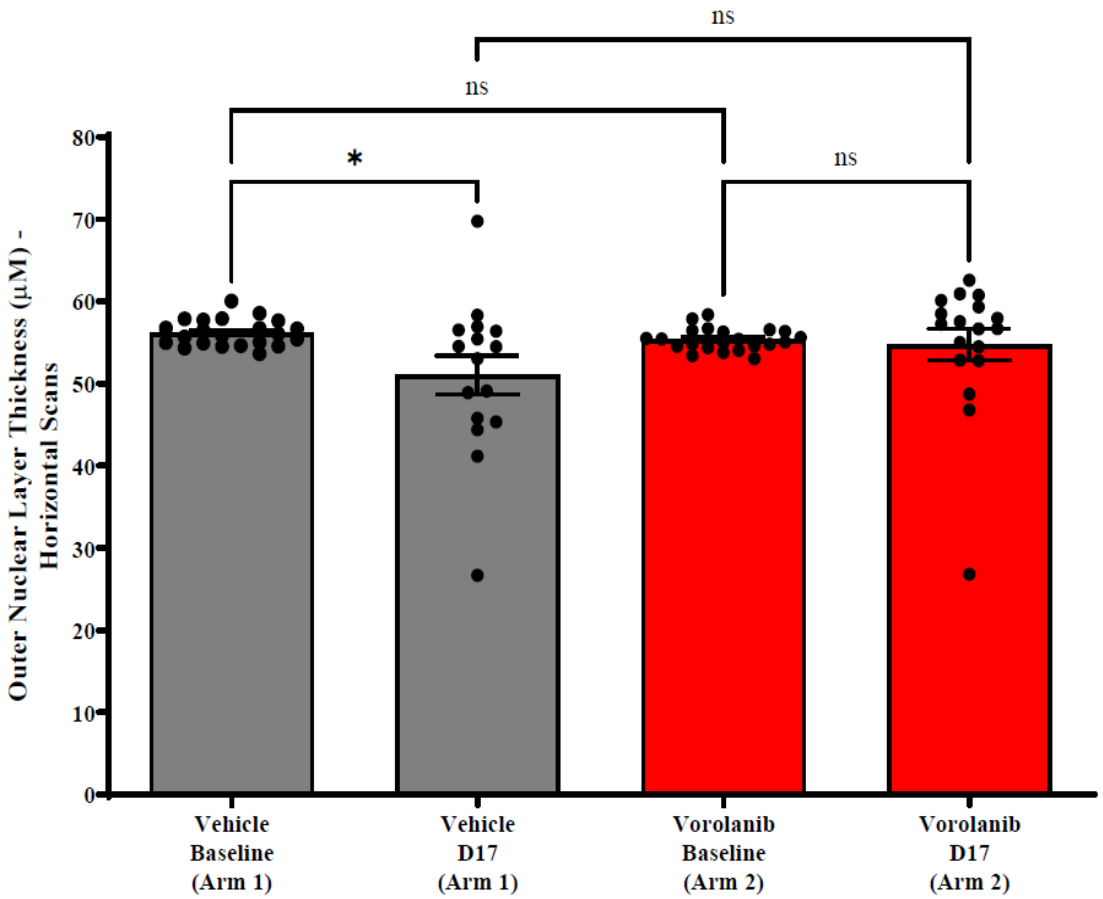
overall loss
of ONL vs control

Mean loss of ONL thickness	
Vehicle	**Vorolanib**
9%	1%

p value = 0.0386
(statistically significant for ONL loss in vehicle arm)

The data was analyzed for significance using a 1-way ANOVA with Sidak's multiple comparison post-test for the indicated pair-wise comparison. Measurements taken at ~3 µm increments across the entire scan from nasal to temporal retina are plotted on the line graph. Results are expressed as Mean and SEM.

Retinal thickness measured by vertical and horizontal OCT scans



Vorolanib has a protective effect on visual acuity

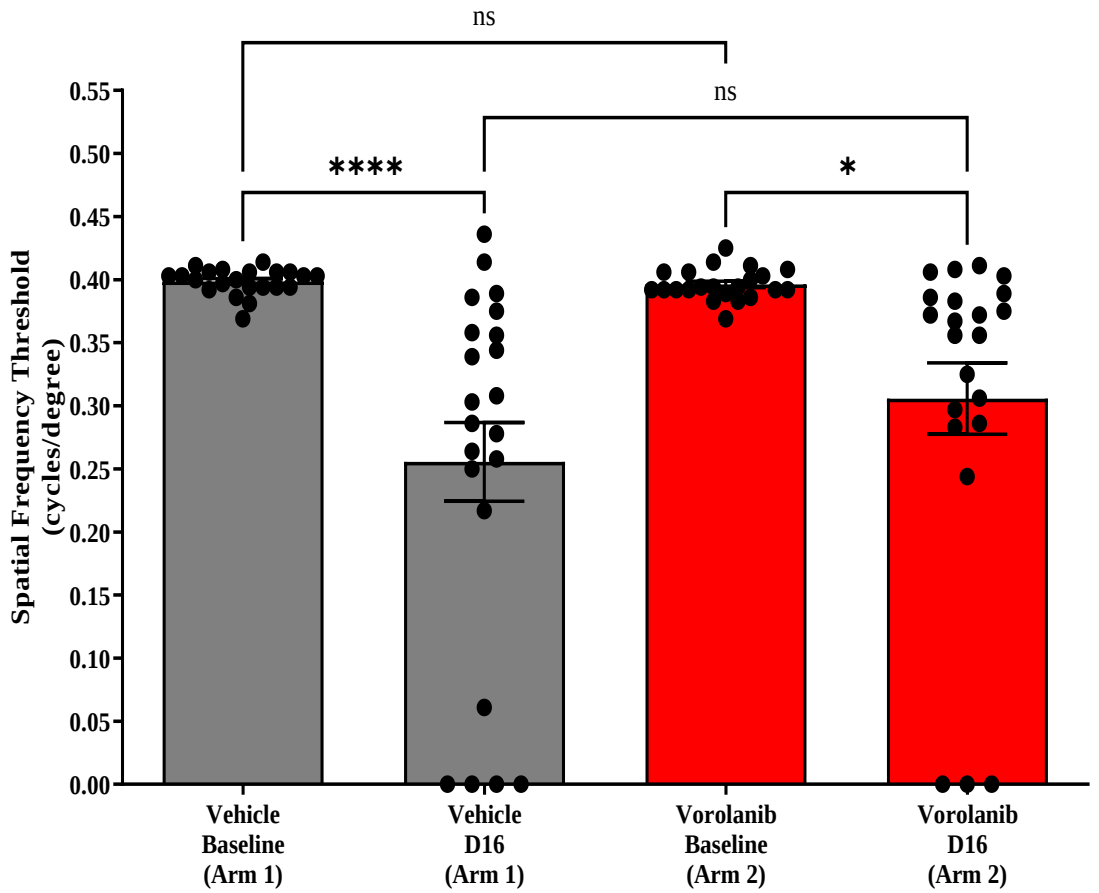
13%

reduction in loss
of visual acuity vs control

Mean loss in visual acuity	
Vehicle	**Vorolanib**
36%	23%

p value = 0.3342
(not statistically significant)

Mean Change in Visual Acuity at Day 16 from Baseline in Animals Treated with Vorolanib vs Vehicle Control



The data was analyzed for significance using a 1-way ANOVA with Sidak's multiple comparison post-test for the indicated pair-wise comparison. Results are expressed as Mean and SEM.

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Vorolanib demonstrates a reduction in fibrosis and retinal atrophy

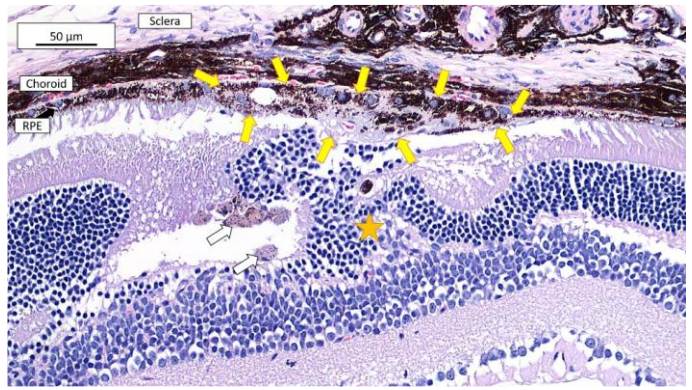
Dose (mg/kg)	0	40
Number of Eyes Examined	**11**	**11**
Fibroplasia, Subretinal	**5**	**2**
(Minimal)	(0)	(1)
(Mild)	(5)	(1)
Atrophy, Retina	**4**	**2**
(Minimal)	(0)	(1)
(Mild)	(4)	(1)

27%

reduction in incidence of subretinal fibroplasia vs control

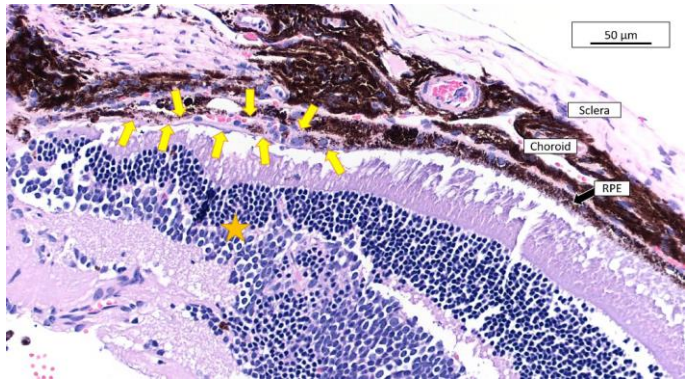
18%

reduction in incidence of retinal atrophy vs control



Yellow arrows indicate **mild** subretinal fibroplasia

Vehicle Treated

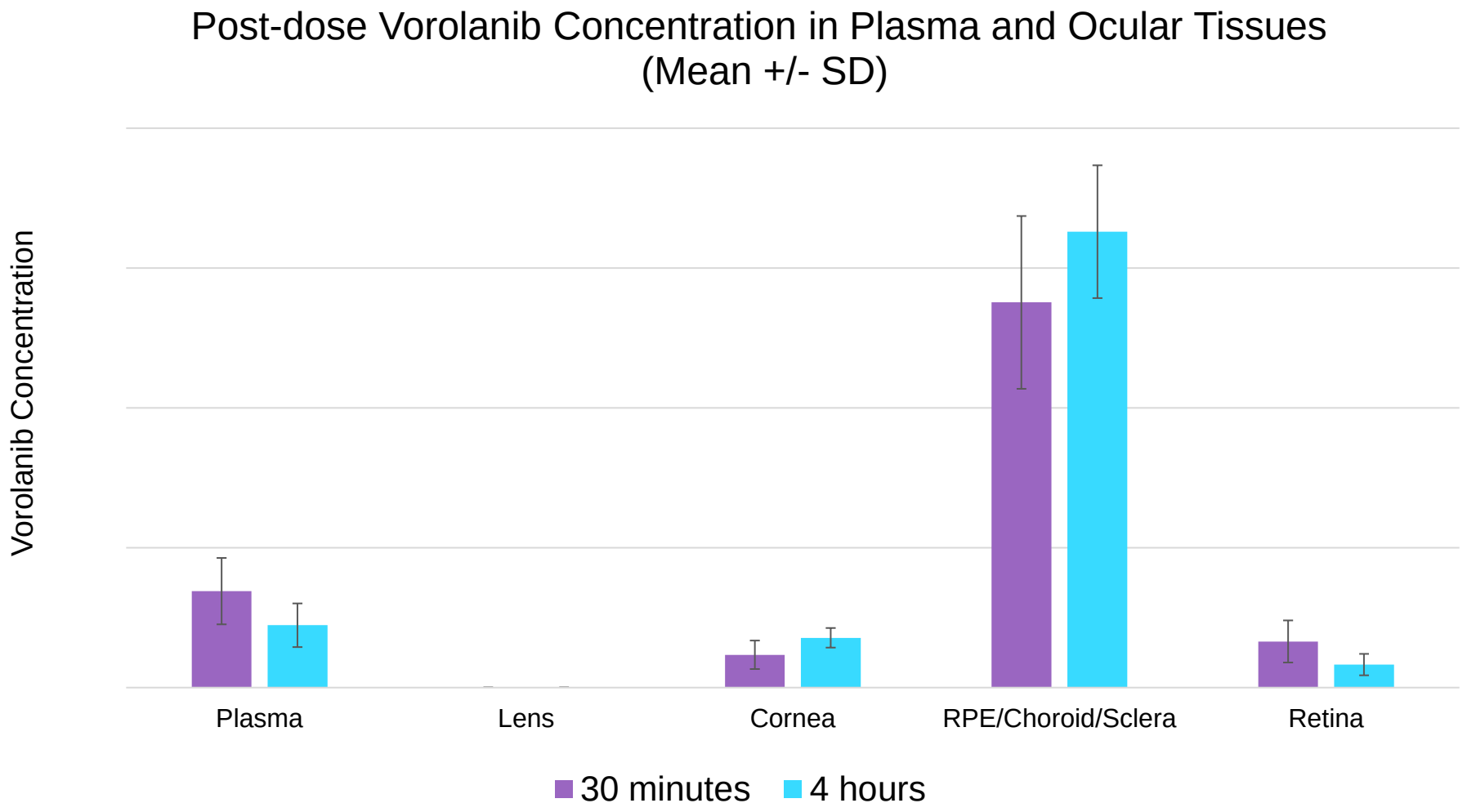


Yellow arrows indicate **minimal** subretinal fibroplasia

Vorolanib Treated

Vorolanib reaches therapeutic levels in ocular tissues within *30 minutes

* First timepoint collected



Summary and Conclusions

***34%**
reduction in loss of contrast vision vs control

****<1%**
overall loss of ONL thickness vs control

13%
reduction in loss of visual acuity vs control

27%
reduction in incidence of subretinal fibroplasia vs control

18%
reduction in incidence of retinal atrophy vs control

*** Statistically significant**
**** Vehicle arm showed statistically significant 9% loss of ONL thickness, while vorolanib arm did not.**

Vorolanib demonstrates the ability to provide retinal neuroprotection and reduction of retinal fibrosis and atrophy in this preclinical model

Discussion

In this study, the beneficial effects of vorolanib on anatomical and functional vision are demonstrated.

The potential to protect the neuroretina from insult associated with chronic retinal neovascular disease through consistent daily treatment may provide meaningful long-term preservation of visual function.

EyePoint is developing vorolanib as Durasert E, a sustained release, bioerodable intravitreal insert employing the Durasert technology and has the potential to provide:

- 6 months or longer of reliable and consistent zero-order release and local tissue exposure
- Consistent daily microgram dose at a therapeutical level
- Potential for longer durability of treatment and reduction in patient visits

Durasert E is being investigated in ongoing Phase 2 trials in wAMD and diabetic retinopathy, and a Phase 2 trial is planned in Diabetic Macular Edema (DME).