Effects of NQ2030 in a Mouse Oxygen-Induced Retinopathy Model after Topical Administration

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Introduction

Diabetic retinopathy is a common long-term ocular complication in diabetes patients which is characterized by retinal vascular abnormalities, neurodegeneration, and inflammation, ultimately leading to blindness.[1] Current drug treatment options are limited to intravitreal injections and are mainly reserved for more severe stages of the disease.[2]

NQ2030 is a novel, non-steroidal activator of a specific nuclear hormone receptor with anti-inflammatory, neuroprotective, and anti-angiogenic properties. Formulated as eye drops in the water-free EyeSol® delivery platform this technology may allow to deliver this potent drug to retina tissues potentially avoiding systemic side effects and the ability to reduce the burden of intravitreal injections.

A common oxygen-induced retinopathy (OIR) model was chosen to demonstrate anti-angiogenic effects of NQ2030 after topical ocular administration.

Methods

129SVE mouse pups were kept in a normoxic environment from postnatal days 1-7 (P1-7). From P8 to P13, pups were subjected to hyperoxia (75% oxygen) to inhibit retinal vessel growth and induce vessel loss (vaso-obliteration). At P13, animals were returned to a normoxic environment to induce retinal neovascularization until P18. From P13 to P18, mice were administered twice daily with 3 µl of different doses of NQ2030 (low, mid and high dose) or vehicle in a masked fashion.

	Naive	Vehicle	NQ2030 low	NQ2030 mid	NQ2030 high
n	6	16	15	18	20
Mean % Vaso-obliteration	2.78	25.2	22.1	23.2	29.0
SD	0.53	3.36	6.03	4.32	3.47
Significance compared to vehicle (Tukey's multiple comparisons test)	n/a	n/a	ns	ns	ns
Mean % Neovascular area	0.14	15.4	13.3	12.5	11.2
SD	0.06	3.04	3.68	3.72	2.84
Significance compared to vehicle (Tukey's multiple comparisons test)	n/a	n/a	ns	ns	p = 0.0038

Table 1: Statistical parameters for vaso-obliteration and neovascularization measurements

At P18, retina tissues were collected from each eye and processed for Isolectin-B4 staining of retinal vasculature. Images of retinal flatmounts (Figure 1) were analyzed for vaso-obliteration and induced neovascularization. Additionally, a group of three animals without OIR or test item treatment were included in the study as naïve control.

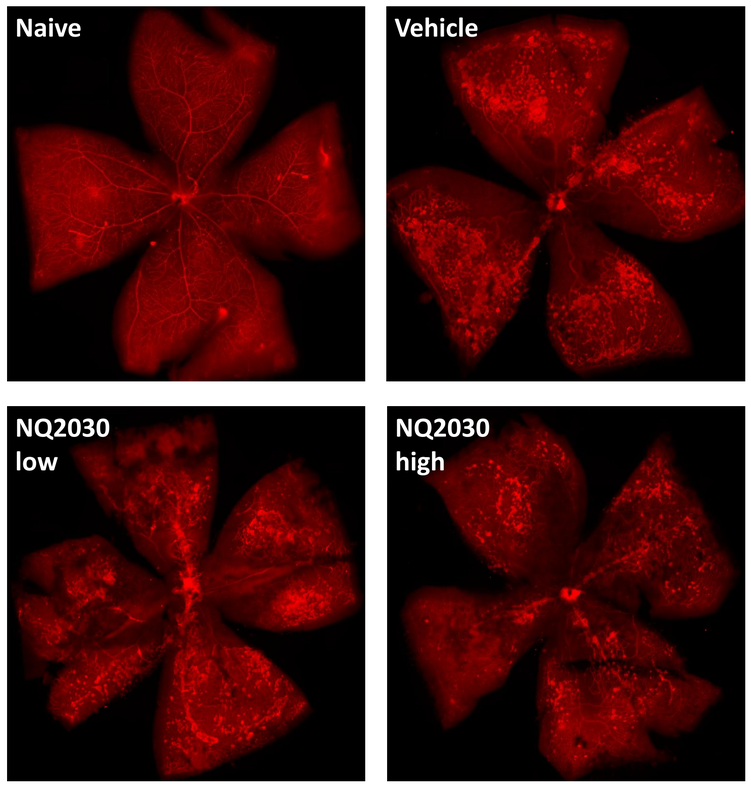

Figure 1: Representative retinal flatmounts for neovascular quantification (naïve, vehicle, NQ2030 low dose, NQ2030 high dose)

Results

Model induction was successfully achieved as oxygen exposure led to a statistically significant increase in both neovascularization and vaso-obliteration in vehicle-treated mice compared to naïve animals. For vaso-obliteration an inverted dose-response relationship was observed, without reaching significance compared to vehicle.

A dose-dependent trend in reduction of neovascularization compared to vehicle was observed in all NQ2030-treated animals (Figure 2). A large variability in body weight of the animals was observed, likely due to intensive handling with twice daily dosing or systemic toxicity. Therefore, neovascularization was analyzed only in a sub-group of animals with similar body weight of 4-7g (n=7-9/treatment group). This analysis showed that the reduction in neovascularization was statistically significant in the highest NQ2030 dose group compared to vehicle (p<0.005) (Table1).

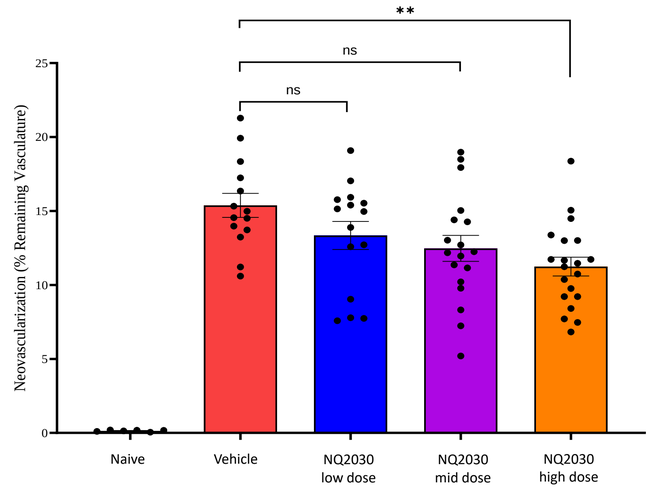

Figure 2: Analysis of Neovascularization (Mean±SEM; **, p=0.0038, 1-Way ANOVA with Tukey's post-test)

Conclusions

- **Twice daily topical administration of NQ2030 reduced the severity of neovascularization in a dose-dependent manner in a common preclinical OIR model**
- **The observed effects confirmed that the API reached the target tissue in relevant concentrations after topical dosing**
- **No signs of ocular irritation were observed**

The results of this study indicate the potential of NQ2030 formulated in EyeSol® as a new topical treatment option for diabetic retinopathy.

References: 1) Shah et al. Diabetic Retinopathy: research to clinical practice. Clin Diabetes Endocrinol. (2017) 3:9 **2)** AAO, Diabetic Retinopathy Preferred Practice Pattern 2024

Disclosures: M. Lambros (contracted by Novaliq); J. Korward, T. Smiatek and F. Dautzenberg (employees of Novaliq)

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