Evaluating the Effects of QLS-111, a Novel Ocular Hypotensive Agent, on Safety, Tolerability, Toxicokinetic Profile, and Reproductive Health in Preclinical Animal Models

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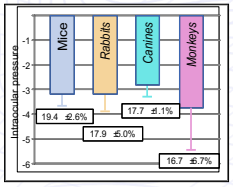
PURPOSE

To evaluate the safety, tolerability, toxicokinetics, and reproductive safety of QLS-111 following chronic ocular administration in preclinical animal models.

INTRODUCTION

- Elevated intraocular pressure (IOP) is the primary modifiable risk factor in glaucoma, with episcleral venous pressure (EVP) setting the physiological floor for IOP lowering[1]
- Current therapies do not directly target EVP, highlighting an unmet need for novel mechanisms of action[1,2]
- ATP-sensitive potassium (K_{ATP}) channel openers have demonstrated consistent IOP lowering effects across mice, rabbits, dogs, and non-human primates (Fig. 1)[3,4,5]



ATP sensitive potassium channel openers lower IOP in various preclinical animal models.

- These effects have been observed in both normotensive and ocular hypertensive models, supporting strong translational relevance[6]
- ATP-sensitive potassium channel openers lower IOP by reducing EVP without affecting other aqueous humor dynamics[5]
- This distinct mechanism enables additive IOP lowering when used in combination with front line therapies[5]
- QLS-111 is a novel ATP-sensitive potassium channel opener designed to directly target EVP and lower IOP, supporting its development as a differentiated ocular hypotensive agent[7]
- The current study evaluates the nonclinical safety, toxicokinetic profile, and reproductive effects of QLS-111 and its active moiety QLS-100 to support clinical development

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METHODS

Chronic Tox – GLP study (Rabbits)

- Dutch-belted rabbits received QLS-111 [0.015% and 0.030% twice daily (BID); 0.075% either BID or three times daily (TID)] in both eyes (OU), for 6 months through ocular topical instillation
- QLS-111-FDC, a fixed dosed combination drug (0.03% or 0.075% QLS-111 with 0.005% latanoprost) was evaluated BID in a separate group
- 28-day recovery period following treatment was included to evaluate reversibility

Chronic Tox – GLP study (Dogs)

- Beagle dogs received topical ocular QLS-111, OU at 0.015% and 0.030% (BID), or 0.075% BID and TID for 9 months through ocular topical instillation
- 28-day recovery period following treatment was included to evaluate reversibility

Assessments (Chronic Tox)

- Mortality, clinical signs, ophthalmic exams, ERG, clinical pathology, toxicokinetics (TK), macroscopic and microscopic pathology were assessed to evaluate safety and tolerability

Embryo-Fetal Development – GLP Study

- Pregnant Sprague-Dawley rats and New Zealand white rabbits were used in this study
- Animals received QLS-100 (active pharmaceutical ingredient of QLS-111) at various concentrations ranging from 0.005 to 0.05 mg/kg/day (rats) or 0.001 to 0.012 mg/kg/day (rabbits) via daily intravenous administration during organogenesis [Gestation day 6-17 (rats) and 7-19 (rabbits)]

Assessments (Embryo fetal development)

- Maternal toxicity: clinical observations, body weight, food consumption
- Pregnancy outcomes: implantation rates, resorptions, fetal mortality
- Fetal endpoints: body weight, morphology, and structural development
- All studies conducted in accordance with regulatory guidance for reproductive toxicology

RESULTS

Chronic Tox Studies

Parameter	Dutch-belted Rabbit		Beagle
	QLS-111	QLS-111-FDC	QLS-111
Overall Tolerability	Well-tolerated; no systemic or ocular toxicity	Well-tolerated; no systemic or ocular toxicity	Well-tolerated; no systemic or ocular toxicity
Clinical/Systemic Findings	No findings	No findings	No findings
Ophthalmic Findings	No findings	Minor, non-adverse conjunctival hyperemia	No treatment-related findings; sporadic and transient mild redness/discharge (non-dose related)
Histopathology	No findings	No findings	No findings
NOAEL	0.135 mg/day (0.075%, TID)	0.090 mg/day (highest dose)	0.135 mg/day (0.075% TID)
Toxicokinetics	Low, dose-proportional exposure; no accumulation	Low, dose-proportional exposure; no accumulation	Low, dose-proportional exposure; no accumulation
TK (NOAEL)	C_{max}: ~1.5 ng/ml; AUC_{tlast}: ~2.5 ng·h/mL	C_{max}: ~0.75 ng/ml; AUC_{tlast}: ~1.7 ng·h/mL	C_{max}: ~2.6 ng/mL; AUC_{tlast}: ~3.3 ng·h/mL

- QLS-111 was well-tolerated across species with no systemic or ocular toxicity observed following chronic dosing up to 9 months
- Rabbits treated with QLS-111-FDC showed similar safety, tolerability and TK profiles
- Low, dose-proportional systemic exposure with no accumulation supports suitability for long-term ocular administration

Embryo-Fetal Development Studies

Parameter	Rat (Sprague Dawley)	Rabbit (New Zealand White)
Maternal Tolerability	Well-tolerated; no clinical or macroscopic findings	Well-tolerated; no clinical findings
Maternal Effects	No effects on body weight or food consumption	No effects on body weight or food consumption
Embryofetal Survival	No effect on implantation, resorptions, or survival	No adverse effects; ↓ trend in post-implantation loss
Fetal Growth	No effect on fetal weight	No effect on fetal weight
Fetal Morphology	No external, visceral, or skeletal malformations	No external, visceral, or skeletal malformations
NOAEL	0.05 mg/kg/day	0.012 mg/kg/day
TK (NOAEL)	C_0: ~43 ng/mL; AUC_{tlast}: ~159 ng·h/mL	C_0: ~6.9 ng/mL; AUC: ~2.7 ng·h/mL

- QLS-100 showed no maternal toxicity, embryofetal toxicity, or teratogenic effects in rats or rabbits
- Reproductive and developmental endpoints were unaffected at all dose levels, supporting a favorable safety profile

CONCLUSIONS

- QLS-111 demonstrated excellent safety and tolerability profiles across species in GLP studies evaluating chronic toxicity and embryo-fetal development
- QLS-111 in fixed dose combination with latanoprost was well tolerated, supporting safe use alongside latanoprost
- QLS-111, with its unique EVP lowering mechanism, excellent safety profile and additive IOP reduction in animal models,[7] shows potential clinical use as monotherapy or in combination as a differentiated ocular hypotensive agent

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SUPPORT

QLARIS BIO

DISCLOSURES

URC, LAB,DJW, LRR, Qlaris Bio Inc. Code E; RAC, TMH, BMW, Qlaris Bio Inc. Code P, E; MPF, Qlaris Bio Inc. Code P, F, C.