



Preclinical assessment of QLS-111, a novel ATP-sensitive potassium channel opener, alone and in combination with approved ocular hypotensive drugs



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INTRODUCTION

- Episcleral venous pressure (EVP) accounts for up to 60% of intraocular pressure (IOP).^{1,2}
- EVP establishes the floor as to how low IOP can be reduced to with current glaucoma medications and minimally invasive glaucoma surgical practices.
- ATP-sensitive potassium channel openers have been shown to lower intraocular pressure (IOP) in several normotensive and ocular hypertensive animal models by specifically targeting EVP.^{3,4}
- Qlaris Bio has developed QLS-111, a novel formulation of an ATP-sensitive potassium channel opener, to selectively target EVP.

AIM

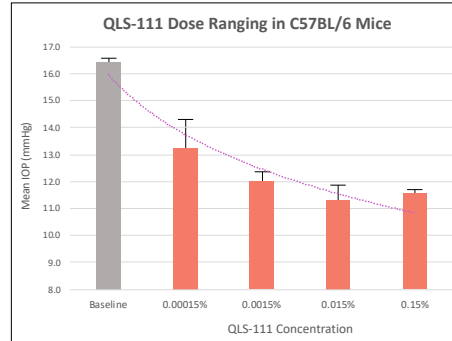
To evaluate the safety, tolerability, and ocular hypotensive properties of QLS-111 in preclinical animal models, either alone or in combination with approved IOP lowering agents.

METHODS

- Optimal effective dose for IOP reduction was determined in C57BL/6J (n=25) mice after treatment with various concentrations of QLS-111 (0.00015%, 0.0015%, 0.015%, 0.15%), once daily for 4 consecutive days, after establishing baseline IOP over 3 days.
- Aqueous humor dynamics parameters (aqueous humor flow rate, trabecular and uveoscleral outflow facility, and EVP) were assessed by constant flow infusion in C57BL/6J mice following 3 consecutive days of once daily treatment with QLS-111 (0.015%) or vehicle.
- Normotensive C57BL/6J mice (n=5 per group) were treated once daily for 4 consecutive days with QLS-111 (0.015%) and timolol maleate (0.5%) alone and in combination – IOP was measured twice daily (4 and 23 hr following treatment) with a handheld rebound tonometer.
- Efficacy of QLS-111-FDC, a novel QLS-111 (0.015%) and latanoprost (0.005%) fixed dose combination formulation, was compared to QLS-111 (0.015%) and latanoprost (0.005%) alone in C57BL/6J mice twice daily (4 and 23 hr following treatment) with a handheld rebound tonometer.
- Safety, tolerability and pharmacokinetic (PK) parameters (half-life, AUC, C_{max}, T_{max}) were assessed in Dutch belted pigmented rabbits using good laboratory practice (GLP) conditions following 28 consecutive days of bilateral, twice daily ocular topical instillation of three doses of QLS-111 (0.03%, n=6; 0.075%, n=6; 0.15%, n=10) or vehicle (n=10).

RESULTS

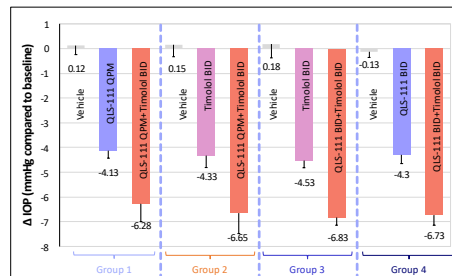
QLS-111 in vivo ocular hypotensive potential and mechanism of action



	QLS-111 Treated (n=4)		Vehicle Treated (n=3)		p-value
	Ave	Stdev	Ave	Stdev	
Baseline IOP (mmHg)	16.5	0.50	16.3	0.30	0.60
Treated IOP (mmHg)	12.3	0.89	16.4	0.49	<0.001
Outflow Facility (μl/min/mmHg)	0.06	0.01	0.04	0.01	0.11
Uveoscleral Outflow (μl/min)	0.05	0.01	0.06	0.02	0.57
Aqueous Flow Rate (μl/min)	0.51	0.15	0.31	0.15	0.15
Episcleral Venous Pressure (mmHg)	4.05	0.42	9.81	1.12	<0.001

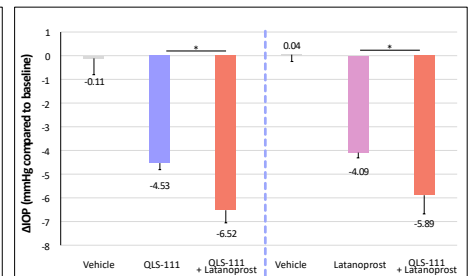
- Maximal IOP lowering efficacy reached with 0.015% QLS-111
- QLS-111 lowered EVP but did not affect other aqueous humor dynamic parameters

Efficacy of QLS-111 and timolol maleate combination therapy



QLS-111 and timolol in combination show up to 2.4 mmHg (p<0.004) of IOP reduction compared to either drug alone.

QLS-111-FDC efficacy compared to QLS-111 and latanoprost alone



QLS-111-FDC lowered IOP by up to 6.5 mmHg from baseline (16.4 ± 0.5 mmHg), which was significantly better than individual therapies (*p<0.003).

Safety, tolerability and toxicokinetic analysis of QLS-111 in Dutch belted rabbits

- Exposure:** Peak plasma levels ≤4.9 ng/mL; non-detectable after 6 hours
- PK:** Half-life ~1.3–2.9 h; AUC and C_{max} rose with dose but less than proportionally
- Accumulation:** No systemic accumulation over time
- Safety:** No drug related adverse events noted in any animals, 5 mM dose (0.06 mg/eye) identified as NOAEL (no observed adverse effect level)

CONCLUSIONS

- QLS-111 is a highly effective ocular hypotensive agent with an excellent safety and tolerability profile in animal models.
- Due to its unique ability to lower EVP, QLS-111 shows significant additive effects with timolol and in a proprietary fixed dose combination with latanoprost (QLS-111-FDC).
- QLS-111 is a novel next generation ATP-sensitive potassium channel opener with enhanced stability and bioavailability and has the potential to be a first-in-class IOP-lowering agent that selectively targets EVP.

DISCLOSURES

- URC, RC, LB, DD, LR, TH and BW are employees of Qlaris Bio.
- Dr. Fautsch is an employee of Mayo Clinic, an advisor to Qlaris Bio, and an inventor on related patents.

REFERENCES

- Selbach JM et al. *Ophthalmologica*. 2005; 219: 357-361.
- Lee SS et al. *J Glaucoma*. 2019 28: 846-857
- Roy Chowdhury U et al. *PLOS ONE*. 2015; 10:e0141783.
- Roy Chowdhury U et al. *IOVS*. 2017; 58: 5731-5742.

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