Ocular Tissue Conversion and Activity Profile of QLS-101, a Novel Topical IOP-Lowering Therapeutic

Cynthia L. Steel, MBA, PhD[1], Hemchand K. Sookdeo, BA[1], Thurein Htoo, MS, MBA[1], Ralph Casale, BS[1], Uttio Roy Chowdhury PhD[2], Michael P. Fautsch, PhD[2], Barbara M. Wirostko, MD, FARVO[1,3]

[1]Qlaris Bio, Inc., Wellesley, MA; [2]Mayo Clinic, Department of Ophthalmology, Rochester, MN; [3]University of Utah, Moran Eye Center, Salt Lake City, UT

Purpose

To evaluate the conversion profile and *in vitro* activity of QLS-101, a novel topical IOP-lowering therapeutic, using human ocular tissues.

Introduction

- Elevated intraocular pressure (IOP) is the only treatable risk factor for glaucoma[1]
- Current treatments for elevated IOP target either aqueous humor production, or aqueous humor outflow through either the trabecular or uveoscleral outflow pathways
- Some K_{ATP} channel openers have demonstrated ocular hypotensive effects in normotensive animals[2-5]
- QLS-101 is being developed as a water-soluble prodrug of a K_{ATP} channel opener
- In preclinical studies, QLS-101 has an excellent tolerability profile (Abstract #353397)
- In this study, we evaluated the ability of QLS-101 to activate K_{ATP} channels, and determined whether QLS-101 can be converted to its active moiety, QLS-100

Methods

Ion Channel Activity

Human embryonic kidney cells stably expressing human $K_{ir}6.2/SUR2B$ K_{ATP} channel subunits were incubated with QLS-101 or QLS-100 (0.003-100 µM), and changes in channel activity were quantified by fluorescence.

Enzymatic Conversion

QLS-101 (5 mM) was incubated at 37°C in Tris buffer (pH 7.4) with either human alkaline phosphatase (ALP), acid phosphatase (ACP), or 5'-nucleotidase (5'-NT) for 15, 30, or 120 minutes. Cleavage was detected with a phosphate detection reagent.

QLS-101 tissue conversion

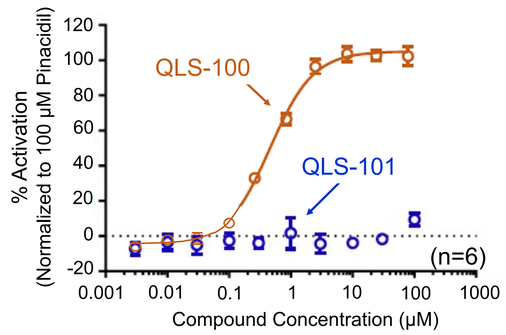
Human donor eyes (70yo Female) were obtained within 9 hours of death, various tissues were isolated, homogenized, and assayed for protein content. Equal amounts of protein were incubated with QLS-101 (10 µM) at 37°C for either 4h or 24h. Quantity of QLS-100 is expressed as a percentage of QLS-101.

Plasma Conversion

Plasma from Sprague Dawley rat, Dutch-belted rabbit, beagle dog, cynomolgus monkey, and human were incubated with 2 µM either QLS-101 or QLS-100 at 37°C. Reactions were quenched at 0, 2h, 4h, 6h, 8h, and 24h, and drug presence quantified by HPLC.

Results

K_{ATP} channel activity of QLS-101 and QLS-100



Test Compound	EC_{50} (µM)
QLS-101	>100 ± NA
QLS-100	0.534 ± 0.05
Cromakalim	1.35 ± 0.12
Pinacidil	5.49 ± 0.99

QLS-100 activates K_{ATP} channels, but QLS-101 does not.

QLS-101 conversion in human ocular tissues

Tissue	Time Point (h)	Percent Conversion
Ciliary Body	4	-
	24	2.55%
Optic Nerve	4	-
	24	0.89%
Iris	4	0.90%
	24	3.93%
Sclera	4	-
	24	1.61%
Retina	4	-
	24	0.74%
Cornea	4	-
	24	0.77%
Trabecular Meshwork	4	-
	24	1.60%

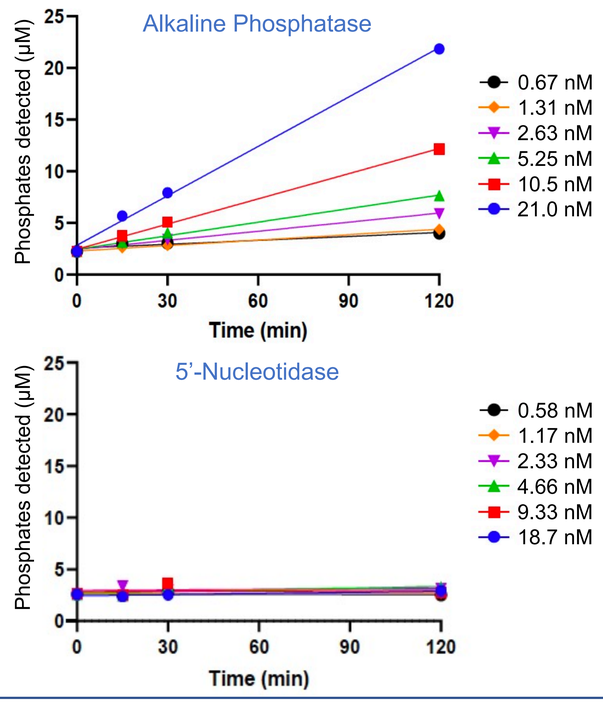
QLS-101 is converted to QLS-100 in human ocular tissues with highest conversion in iris, sclera, and TM.

QLS-101 conversion in plasma

Species	QLS-101 Present (%)		QLS-100 Present (%)		QLS-101 $T_{½}$ (hh:mm)
	0 h	24 h	0 h	24 h	
Sprague Dawley Rat	100%	93.7%	0.2%	0.2%	68:05
Dutch-belted Rabbit	100%	97.3%	0.2%	0.2%	100:12
Beagle Dog	100%	95.4%	0.1%	0.1%	69:52
Cynomolgus Monkey	100%	80.3%	0.2%	0.2%	45:37
Human	100%	81.3%	0.2%	0.1%	32:13

QLS-101 is minimally converted to QLS-100 in plasma from multiple species

Cleavage of QLS-101 by Various Phosphatases *in vitro*



QLS-101 is converted in vitro to QLS-100 by alkaline phosphatase, but not acid phosphatase or 5'-nucleotidase

Conclusions

- QLS-101 is an inactive prodrug, requiring conversion to QLS-100 by alkaline phosphatase to activate K_{ATP} channels
- Conversion of QLS-101 to QLS-100 by ocular tissues supports topical application and local conversion for downstream ocular hypotensive activity

Phase 2 dose-ranging clinical trials utilizing QLS-101 in patients with POAG or NTG are currently ongoing.

References

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Cynthia L. (Pervan) Steel, PhD (csteel@qlaris.bio)