Systemic and Ocular Toxicology and Pharmacokinetic Profiles of QLS-101, a Novel Topical IOP- Lowering Therapeutic

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Purpose

To summarize the potential systemic and ocular toxicity and pharmacokinetic (PK) profiles of QLS-101, a novel topical IOP-lowering therapeutic, when dosed topically in beagle dogs.

Introduction

- Current treatments for elevated IOP target the production of aqueous humor, or outflow facility through either the conventional (trabecular) or unconventional (uveoscleral) pathways.
- Episcleral venous pressure (EVP) constitutes the largest percentage (approximately 50-60%) of total IOP[1] and sets the ”floor” for maximal medical intervention, No current treatments primarily targets EVP. In recent years, several ATP-sensitive potassium channel (K_{ATP}) openers have been shown to have ocular hypotensive properties.[2-5]
- QLS-101, a water-soluble prodrug of an ATP-sensitive potassium channel opener, is being developed by Qlaris Bio, Inc. as an ocular hypotensive agent.
- QLS-101 has been shown to have a novel mode of action that affects distal outflow resistance and episcleral venous pressure.[6]
- In this study, systemic and local side effects of QLS-101 was evaluated following topical instillation of various doses of the prodrug in both eyes of beagle dogs.

Methods

Tolerability assessment following topical ocular administration with QLS-101

- QLS-101 or vehicle was added topically as a 40 µl drop to both eyes (OU) of beagle dogs (age 5-7 months, 3 males and 3 females per group), once daily for 28 days.
  - Vehicle: Isotonic Phosphate-Buffered Saline (pH 6.5)
  - 2%: 0.8 mg/eye/dose
  - 4%: 1.6 mg/eye/dose
  - 8%: 3.2 mg/eye/dose
- Routine clinical assessments that included behavioral observations, food intake, gross clinical observations, IOP, slit lamp, dilated fundus exams and ERGs were performed throughout the treatment period
- At the end of treatment, animals were euthanized, necropsied and select tissues were isolated and prepared for histopathology.

Pharmacokinetic (PK) evaluation of systemically administered QLS-101

- To evaluate systemic maximum tolerated dose (MTD), single escalating doses of QLS-101 (0.05-5.0 mg/kg/day) were administered by IV bolus to one male and one female beagle dog, with a 48h minimum observation period between doses.
- Plasma samples were collected at various timepoints in both studies, concentrations of QLS- 101 and its active moiety QLS-100 were determined by LC/MS-MS, and data was used to generate PK parameters.

Results

Ocular Toxicity for QLS-101 in Beagle Dogs

	QLS-101 Dose			
Observation	0%	**2%**	4%	8%
Slight redness (pre-dose)	3	**0**	0	0
Slight redness (dose-related)	9	**3**	5	10
Slight discharge	0	**0**	1	2
Pinpoint corneal superficial epitheliopathy	1	**0**	0	0
ERGs & Fundus Exams	WNL	**WNL**	WNL	WNL

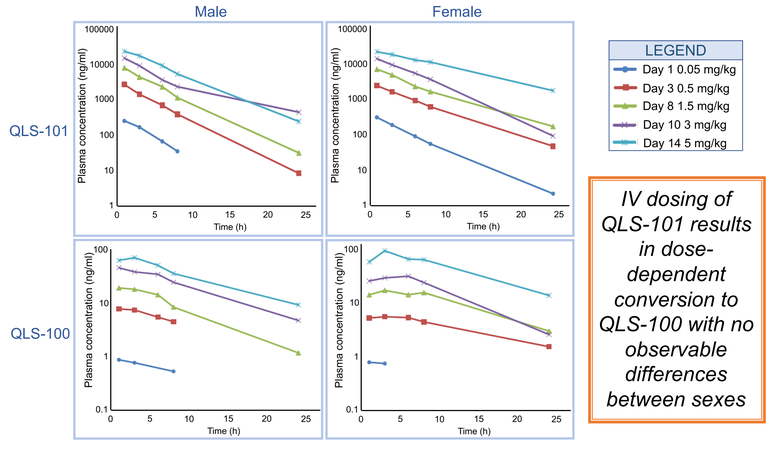
No changes were observed with 2% QLS-101, the highest planned dose for clinical trials. Only at 8% QLS-101 did several clinical observations exceed those observed at baseline (WNL: within normal limits)

Systemic Toxicity for Topical QLS-101

Assessments	Result
Mortality	None
Clinical Observations	None
Significant loss of body weight	None
Decreased food consumption	None
Hematology	None
Coagulation parameters	None
Clinical Chemistry	None
Macroscopic pathology	None
Organ weights	None

QLS-101 is well-tolerated systemically when dosed once daily up to 8% OU

QLS-101 Single IV Pharmacokinetic Profile



IV dosing of QLS-101 results in dose-dependent conversion to QLS-100 with no observable differences between sexes

Pharmacokinetic parameters of topical QLS-101

Pharmacokinetic Parameters		QLS-101 Dose					
		2.0%		4.0%		8.0%	
		Male	Female	Male	Female	Male	Female
QLS-101 (prodrug)							
C_{max} (ng/mL)	Day 1	36.5	55.5	73.7	129	166	156
	Day 28	47.0	80.2	57.3	201	**147**	**139**
$AUC_{0\text{-last}}$ (ng•h/mL)	Day 1	231	496	520	1220	1520	1480
	Day 28	272	545	381	1750	**1260**	**1200**
T_{max} (h)	Day 1	1	2	1	2	2	2
	Day 28	1	2	1	2	2	2
$t_{½}$ (h)	Day 1	3.69	4.12	4.26	6.18	4.82	4.92
	Day 28	3.44	3.68	3.32	4.95	5.08	5.15
QLS-100 (active moiety)							
C_{max} (ng/mL)	Day 1	25.3	25.1	24.4	23.2	76.0	72.2
	Day 28	10.6	18.4	15.5	19.9	**31.0**	**32.9**
$AUC_{0\text{-last}}$ (ng•h/mL)	Day 1	99.8	92.7	133	125	361	294
	Day 28	49.1	80.1	70.7	105	**166**	**154**
T_{max} (h)	Day 1	2	2	4	2	2	2
	Day 28	2	2	2	2	2	2
$t_{½}$ (h)	Day 1	3.64	2.65	3.24	3.61	3.44	2.73
	Day 28	2.35	2.51	3.12	2.06	3.38	4.90

Based on these data, overall low severity levels and lack of noteworthy adverse effects, the no-observed-adverse-effect level (NOAEL) was determined to be 8%.

Summary

- QLS-101 dosed topically once daily was well-tolerated with an NOAEL of 8.0%.
- No mortality, change in body weight or food consumption were noted.
- Histological examination showed no toxicity as a result of QLS-101.
- Maximum tolerated dose was determined to be 3 mg/kg, which corresponded to sex-combined C_{max} and AUC T_{last} values of 16.4 µg/mL and 106.55 µg*h/mL for QLS-101, and 35.5 ng/mL and 431 ng*h/mL, for QLS-100.

Conclusions

QLS-101, when dosed topically OU QD for 28 days in beagle dogs, is a well-tolerated ocular hypotensive agent and may be considered for further trials in human subjects as a potential therapeutic for lowering IOP.

References

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