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

Barbara M. Wirostko, MD\textsuperscript{1,2}, Hemchand K. Sookdeo, BA\textsuperscript{1}, Thurein Htoo, MS, MBA\textsuperscript{1}, Ralph Casale, BS\textsuperscript{1}, Uttio Roy Chowdhury, PhD\textsuperscript{2}, Michael P. Faustch, PhD\textsuperscript{2}, Cynthia L. Steel, MBA, PhD\textsuperscript{1}
\textsuperscript{1}Qlaris Bio, Inc., Wellesley, MA; \textsuperscript{2}Department of Ophthalmology, Mayo Clinic, Rochester, MN; \textsuperscript{3}University of Utah, Moran Eye Center, Salt Lake City, UT

\section*{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\textsuperscript{1} and sets the “floor” for maximal medical intervention. No current treatments primarily targets EVP. In recent years, several ATP-sensitive potassium channel (K\textsubscript{ATP}) openers have been shown to have ocular hypotensive properties.\textsuperscript{2,3}

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.\textsuperscript{4}

QLS-101 has shown to have a novel mode of action that affects distal outflow resistance and episcleral venous pressure.\textsuperscript{5}

In this study, systemic and local side effects of QLS-101 were evaluated following topical instillation of various doses of the prodrug in both eyes of beagle dogs.

\section*{Methods}

\subsection*{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.

\subsection*{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.

\section*{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.

\section*{Results}

\subsection*{Ocular Toxicity for QLS-101 in Beagle Dogs}

<table>
<thead>
<tr>
<th>Observation</th>
<th>QLS-101 Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0%</td>
</tr>
<tr>
<td>Slight redness (pre-dose)</td>
<td>3</td>
</tr>
<tr>
<td>Slight redness (dose-related)</td>
<td>9</td>
</tr>
<tr>
<td>Slight discharge</td>
<td>0</td>
</tr>
<tr>
<td>Pinpoint corneal superficial epithelopathy</td>
<td>1</td>
</tr>
<tr>
<td>ERGs &amp; Fundus Exams</td>
<td>WNL</td>
</tr>
</tbody>
</table>

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).

\subsection*{Systemic Toxicity for Topical QLS-101}

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>None</td>
</tr>
<tr>
<td>Clinical Observations</td>
<td>None</td>
</tr>
<tr>
<td>Significant loss of body weight</td>
<td>None</td>
</tr>
<tr>
<td>Decreased food consumption</td>
<td>None</td>
</tr>
<tr>
<td>Hematology</td>
<td>None</td>
</tr>
<tr>
<td>Coagulation parameters</td>
<td>None</td>
</tr>
<tr>
<td>Clinical Chemistry</td>
<td>None</td>
</tr>
<tr>
<td>Macroscopic pathology</td>
<td>None</td>
</tr>
<tr>
<td>Organ weights</td>
<td>None</td>
</tr>
</tbody>
</table>

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

\subsection*{QLS-101 Single IV Pharmacokinetic Profile}

\section*{Pharmacokinetic parameters of topical QLS-101}

\begin{center}
\begin{tabular}{|c|c|c|c|c|c|}
\hline
QLS-101 Dose & 2% & 4% & 8% \\
\hline
\hline
Day 1 & Day 2 & Day 28 \\
\hline
\hline
\textbf{C_{\text{max}} (ng/mL)} \\
\hline
101 & 101 & 101 \\
\hline
\textbf{AUC_{0-\text{last}} (ng•h/mL)} \\
\hline
101 & 101 & 101 \\
\hline
\textbf{T_{1/2} (h)} \\
\hline
101 & 101 & 101 \\
\hline
\textbf{T_{\text{last}} (h)} \\
\hline
101 & 101 & 101 \\
\hline
\textbf{t_{\text{last}} (h)} \\
\hline
101 & 101 & 101 \\
\hline
\end{tabular}
\end{center}

\section*{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-100.

Maximum tolerated dose was determined to be 3 mg/kg, which corresponded to sex-combined C\textsubscript{max} and AUC\textsubscript{0-\text{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.

\section*{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.

\section*{References}
2. Roy Chowdhury U et al. PLOS ONE. 2015;10:e0141783

\section*{Copyright/Contact}
© Qlaris Bio, Inc. 2021 (www qlaris bio) Barbara M. Wirostko, MD, FARVO (bewirostko@qlaris bio)