Topical Ocular Laquinimod in Development for Inflammatory Eye Disorders

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PURPOSE

Laquinimod (LAQ) is a first-in-class immunomodulator which activates the aryl-hydrocarbon receptor. During years of advanced product development, clinical efficacy and safety data on an oral formulation of LAQ have been established in more than 5,000 patients with autoimmune diseases, primarily multiple sclerosis (MS). LAQ has shown therapeutic potential in uveitis based on preventive and inhibitory effects on ocular inflammation in animal models.[1,2]

A pharmaceutical formulation optimized for ocular absorption of LAQ has been developed and its ocular tolerability confirmed in rabbit at daily doses 5-fold higher than in man (unpublished data). The present studies were designed to evaluate the overall safety and ocular tolerability of topical ocular LAQ in humans, and intra-ocular distribution of LAQ in rabbits.

CONCLUSIONS

- This was the first time a topical ocular (eye-drop) formulation of LAQ was administered to humans
- LAQ eye drops at 10 mg/mL were safe and tolerable in healthy subjects following unilateral administration of single doses up to 1.2 mg and multiple doses up to 0.6 mg once daily for 21 days
- LAQ eye drops demonstrated intraocular distribution in rabbits
- Collectively, these results warrant clinical studies in patients with inflammatory eye disorders

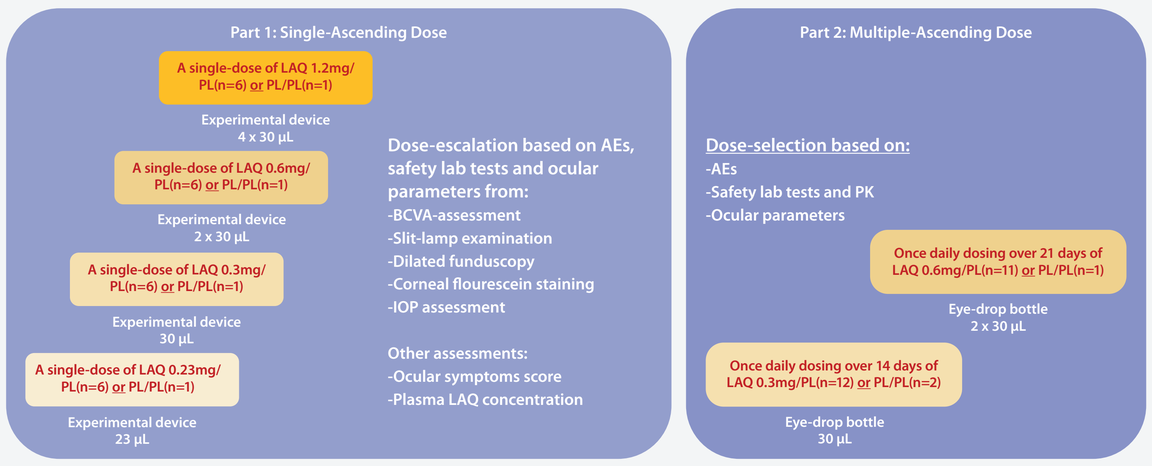
Safety and Tolerability in Humans – Clinical Phase I Study

METHODS

Healthy subjects (54 men) at the age of between 18 and 35 years were enrolled into a randomized, placebo-controlled, double-masked, subsequent group study at the Department of Clinical Pharmacology, Medical University of Vienna, Austria. The primary objective of the study was to assess the safety and tolerability of single- and multiple ascending doses (SAD/MAD) of LAQ eye drops.

The 10 mg/mL formulation of laquinimod (LAQ) was administered as a unilateral single dose of 0.23, 0.3, 0.6, or 1.2 mg, or as a unilateral multiple dose of 0.3 or 0.6 mg once daily for 14 days (0.3 mg) or 21 days (0.6 mg) (Figure 1). In each dose-group, the subjects were randomized at a 6:1 ratio to receive LAQ or placebo. For subjects randomized to receiving LAQ, further randomization on the eye level (right/left eye) was undertaken and placebo administered in the contralateral eye. For subjects randomized to receiving placebo only, placebo was administered in both eyes. Adverse events (AEs), standard eye exams and ocular symptoms were assessed.

Figure 1. Clinical Phase I study design.



RESULTS

- LAQ eye drops were generally well tolerated by the subjects in all the study groups
- For treatment emergent adverse events related to LAQ, see Table 1
- All AEs resolved before study completion
- No serious AEs were reported
- No clinically meaningful changes in the anterior segment of the eye were identified using slit lamp
- No clinically meaningful changes in ocular symptoms, visual acuity, corneal epithelium, intraocular pressure or retinal surface were identified
- Assessments of blood pressure, heart rate and commonly used blood chemistry did not reveal any clinically significant systemic AEs

Table 1. Adverse events related to LAQ

Dosage regimen	Adverse event	Severity	Outcome
0.23 mg single dose	N/A		
0.3 mg single dose	N/A		
0.6 mg single dose	N/A		
1.2 mg single dose	Increased fluorescein staining (in both eyes)	Mild	Resolved
0.3 mg multiple dose	Vital dye staining of the cornea	Mild	Resolved
0.6 mg multiple dose	Headache	Moderate	Withdrawal

Eye Tissue Concentrations of LAQ in Rabbits – Non-clinical Study

METHODS

This was a Quantitative Distribution Study performed to assess the intraocular distribution of LAQ after topical administration of the 10 mg/mL eye-drop formulation of LAQ. Albino rabbits (5 male animals) received daily doses of 0.9 mg LAQ in each eye for 6 days. On Day 7, following administration of 0.3 mg LAQ, the animals were sacrificed one at a time at five time-points post-dose. The rabbit eyes were enucleated and LAQ quantified in eye sections using MALDI imaging.

RESULTS

- LAQ was detected at high concentrations in cornea and surrounding tissue +30 min post-dose and at low concentrations at the later time-points
- LAQ was also detected in retina/choroid at +4 h and +8 h post-dose, and in sclera at +8 h post-dose at concentrations similar to those in plasma (Table 2)

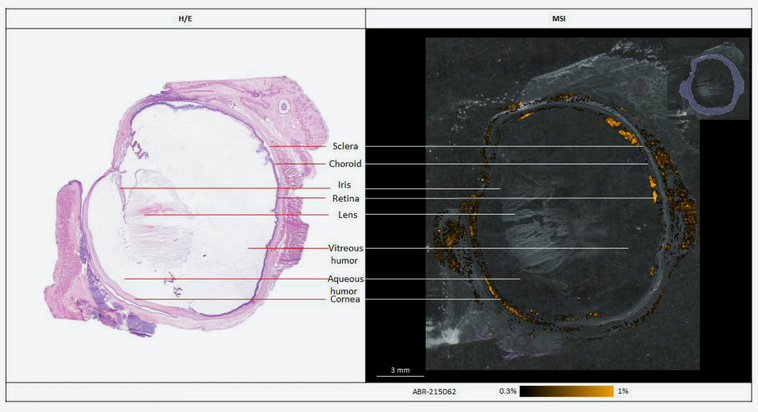
Intraocular concentrations of LAQ following topical ocular administration of 0.3 mg LAQ in each eye given as eye drops (10 mg/mL)

QMSI= Quantitative Mass Spectrometrical Imaging; LOD= Limit of Detection (1.23 µM); BLOD= Below Limit of Detection; LLOQ= Lower Limit of Quantification (3.9 µM); BLLOQ - (Below Lower Limit of Quantification)

Table 2. Intraocular concentrations of LAQ

Animal ID	Sampling time (post-dose Day 10)	ROI in right eye (ROI=Region of Interest)	QMSI (µM)	Plasma conc. (µM)
007M	30 min	Retina/choroid Sclera Cornea Surrounding tissue	BLOD BLOD 243.93 78.32	13.0
012M	1 h	Retina/choroid Sclera Cornea Surrounding tissue	BLOD BLOD 30.37 22.53	16.8
009M	2 h	Retina/choroid Sclera Cornea Surrounding tissue	BLOD BLOD BLLOQ BLLOQ	12.6
010M	4 h	Retina/choroid Sclera Cornea Surrounding tissue	10.37 BLLOQ 13.5 11.7	7.2
011M	8 h	Retina/choroid Sclera Cornea Surrounding tissue	9.87 13.99 16.30 24.07	7.8

Figure 2. Intraocular distribution of LAQ as measured by Maldi Imaging



Distribution of LAQ at 8 hours after topical administration showing a high concentration of LAQ in the posterior part of the eye. To the left a H/E staining of the section, to the right the MSI acquisition. Note that due to pixel number limitations the MSI acquisition includes the cornea, sclera, choroid, retina and surrounding areas. MSI acquisition area is delineated in the top right panel.

References:
1. Xu B, Jia X, Tang J, Caspi RR, Gery I. Laquinimod effectively inhibits development of EAU and its associated immune effector responses. Invest Ophthalmol Vis Sci 2019;60:ARVO E-Abstract 792.
2. Xu B, Jia X, Tang J, Caspi RR, Gery I. Laquinimod arrests development of experimental autoimmune uveitis (EAU) and inhibits related immune processes, in the context of altered gut microbiota. J Immunol 1 May 2020; 204 (1 Supplement): 150.18. https://doi.org/10.4049/jimmunol.204.Supp.150.18.

Financial interest
GG: Scientific advisor to Active Biotech; EB, PE, HT, MT and EV: Employed by Active Biotech and shareholders in Active Biotech; DS: Nothing to declare.