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Safety, Tolerability, and Distribution of Topical Laquinimod Ophthalmic Solution, an Innovative Immunomodulator Targeting Aryl Hydrocarbon Receptor (AHR): Primary Outcomes of the LION Study

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Financial Disclosure

- **Presenter:** Dalia El-Feky

I have no financial interests or relationships to disclose

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I have no financial interests or relationships to disclose

- Investigational medicinal product (IMP) was provided by Active Biotech

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Background

- Topical corticosteroids are often used in the management of ocular inflammation, however there is high risk of clinically significant toxicities

- Laquinimod (LAQ) is a first-in-class synthetic small-molecule immunomodulator that targets the aryl hydrocarbon receptors (AhR) in the antigen presenting cells and skews the immune response towards an anti-inflammatory phenotype

- Phase II and III studies of **oral LAQ (0.6 mg daily) for multiple sclerosis (MS)** revealed a favorable safety and tolerability profile based on over 14000 patient-years of exposure

Background

- Topical ocular formulation of laquinimod (LAQ) has been optimized by Active Biotech to reach the posterior part of the eye

- **In uveitis models**, topical LAQ (eyedrop) demonstrated **a significant, dose-dependent reduction of uveitis** with **measurable concentrations of LAQ in the posterior part** of the eye

- A phase 1 randomized, placebo-controlled, double-masked study of once daily LAQ eyedrop (0.6 mg) for 21 days in **healthy participants** demonstrated **no clinically meaningful ocular or systemic adverse events**

Objective

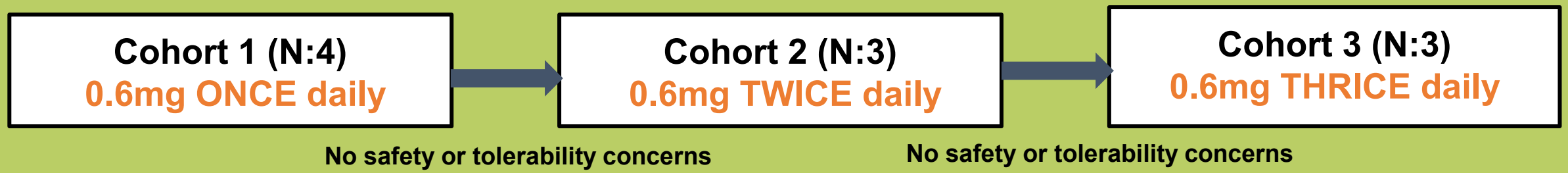
- **Prospective, open-label, dose escalation phase I clinical trial**
- Conducted by the Uveitis Division at the Byers Eye Institute, Stanford University (Palo Alto, California, USA)
- To assess the safety and tolerability of laquinimod eye-drops and explore its ocular distribution in aqueous, vitreous as well as plasma

Methods

- Key inclusion criteria: 18 years or older subject, scheduled to undergo pars plana vitrectomy for various aetiologies
- Key exclusion criteria: Active periocular or ocular infectious disease, prior ocular surgery or intravitreal steroids within 90 days, intravitreal anti-VEGF within 30 days, topical calcineurin inhibitors within 2 weeks, strong inhibitors/inducers of CYP3A4 within 2 weeks, hepatic, renal or cardiac impairment
- Sampling of anterior chamber (AC) fluid, vitreous, and plasma within 60 minutes post-surgery

Methods

- Ten patients undergoing vitrectomy, enrolled in three subsequent dose-escalation cohorts (0.6, 1.2, and 1.8 mg per day) and received laquinimod eye drops (10 mg/mL) for 14 days prior to the surgery



- Laquinimod concentration measured in the undiluted aqueous and vitreous as well as plasma samples

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Results

- Laquinimod (LAQ) eye drop was well-tolerated across the three doses without medication related-adverse events, assessed by BCVA, ocular examinations, multimodal imaging, CBC, CMP and EKG
- LAQ was detected in aqueous, vitreous and plasma samples with the following free (unbound) concentrations

Dose (mg/day)	**Aqueous** mean (nM)	**Vitreous** mean (nM)	**Plasma** mean (nM)
0.6	998	13	8
1.2	4022	55	16
1.8	7141	76	27

Abbrev. BCVA – Best Corrected Visual Acuity, SD-OCT – Spectral Domain-Optical Coherence Tomography, CBC – Complete Blood Count, CMP – Complete Metabolic Panel, EKG - Electrocardiogram

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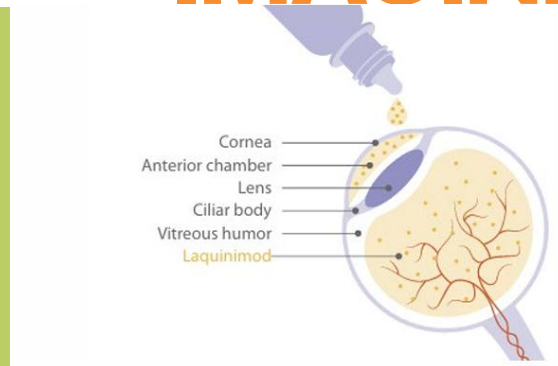
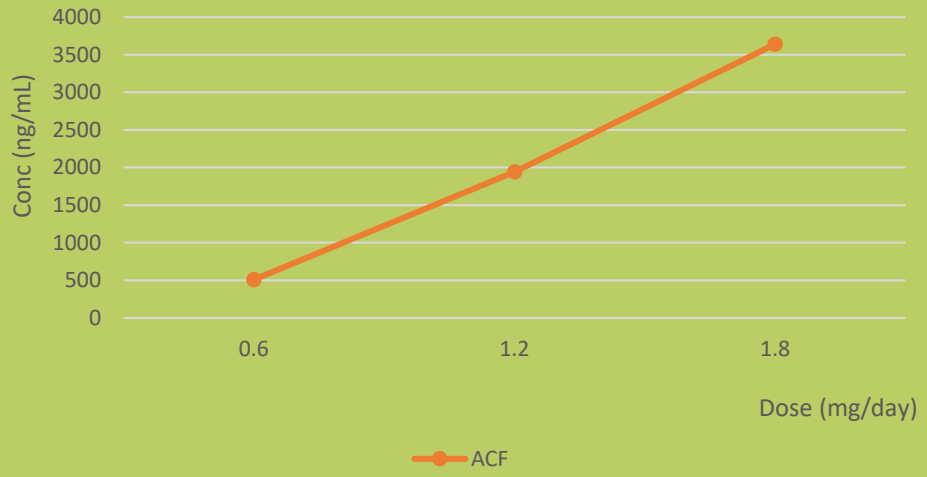
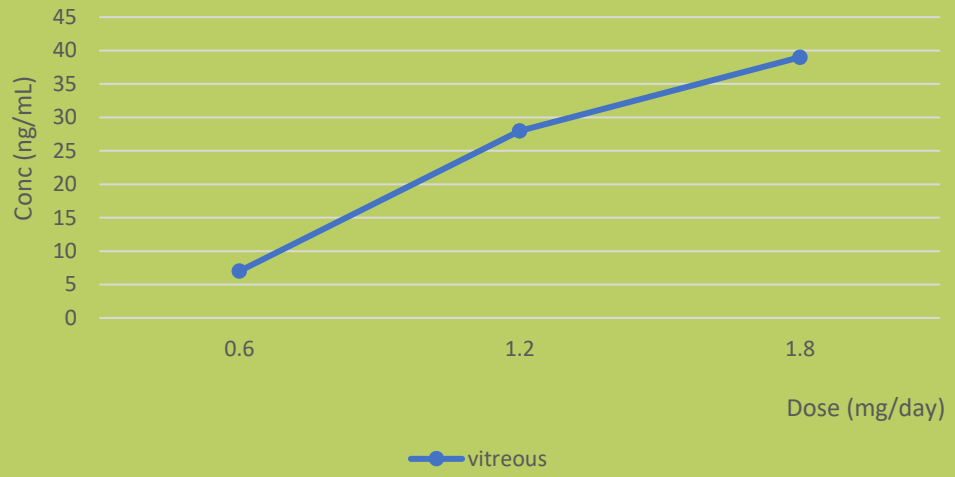
Results







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Conclusion

- Topical laquinimod (10 mg/ml) for 14 days was safe and well-tolerated at daily doses of 0.6, 1.2, and 1.8 mg, with dose-dependent drug levels detected in the vitreous and aqueous

- The concentrations **quantified in the vitreous could be therapeutically relevant in all doses**

- These findings support further investigation of its therapeutic potential in uveitis and other ocular inflammatory diseases

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