Safety, Tolerability, and Distribution of Topical Laquinimod Eye Drops: Primary Outcomes of the LION Study

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INTERNATIONAL OCULAR INFLAMMATION SOCIETY

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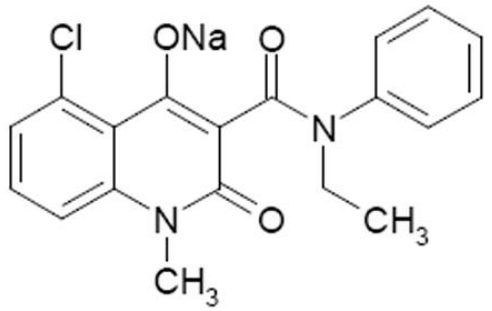
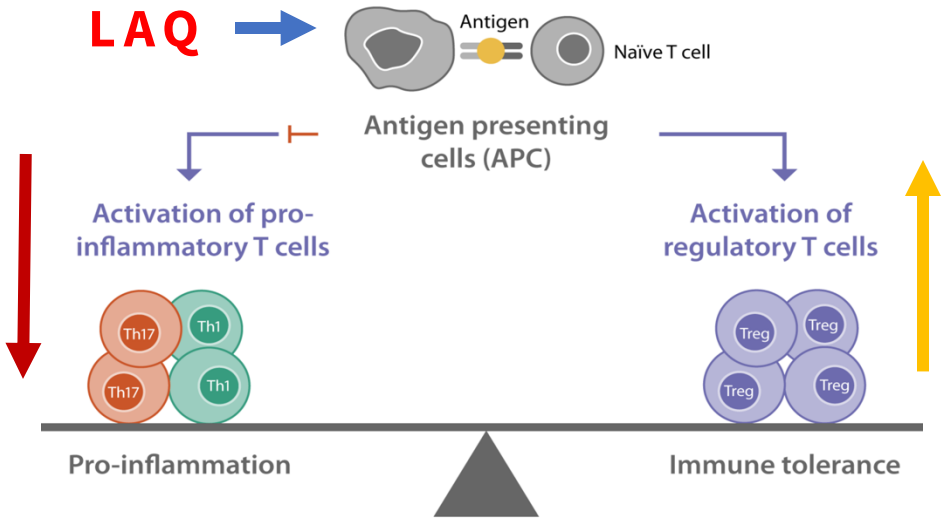
Disclosure

- The LION Study was administratively sponsored by the Global Ophthalmic Research Center (Los Altos, CA)
- Investigational medicinal product (IMP) was provided by Active Biotech

Laquinimod (LAQ)



- Developed by Active Biotech
- A first-in-class synthetic small-molecule immunomodulator
- Targets the aryl hydrocarbon receptors (AhR) in the antigen presenting cells



LAQ skews the immune response towards an anti-inflammatory phenotype

Abbr: AhR – Aryl hydrocarbon Receptor, APC- Antigen Presenting Cell, T reg-Regulatory T cell, Th 1-T helper cell 1, Th17-T helper cell 17

References: Kaye et al Proc Natl Acad Sci U S A. 2016 Oct 11;113(41):E6145-E6152, Xu et al J Immunol (2020) 204 (1_Supplement): 150.18

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ORAL LAQ IN CNS DISEASES

- **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 14 000 patient-years of exposure
- Immunomodulator & neuroprotective with significant outcomes on relapse-related endpoints
- Headache, arthralgia and asymptomatic mild elevation of liver enzymes were the most common noted systemic adverse events

* **References:** Comi G. et al., Mult Scler. 2022 Apr;28(4):608-619 11;13524585211032803. Vollmer T. L. et al., J Neurol. 2014; 261(4): 773-83
Comi G. et al., N Engl J Med. 2012 Mar 15;366(11):1000-9

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TOPICAL ANTI-INFLAMMATORY: AN UNMET NEED

- **Topical corticosteroids** are often used in the management of inflammation of the anterior segment of the eye
- High risk of **clinically significant toxicities**

- The topical ocular formulation of LAQ has been developed by Active Biotech and optimized to reach the posterior part of the eye with the goal of investigating its therapeutic potential in ocular inflammatory diseases as a **steroid sparing therapy**

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PRE-CLINICAL STUDIES OF TOPICAL LAQ

- In uveitis models, topical (eyedrops) and oral (by gavage) LAQ demonstrated **a significant, dose-dependent reduction of uveitis**
- Different models for eyes with excessive neovascularization (corneal and macular), illustrated that LAQ might **reduce vessel formation** in the eye
- Remarkably, measurable concentrations of LAQ in the posterior part of the eye were detected along with lower systemic exposure compared to oral therapy

References: * Xu B, Jia X, Tang J, et al. Laquinimod effectively inhibits development of EAU and its associated immune effector responses. Invest Ophthalmol Vis Sci. 2019;60
* Xu B, Jia X, Tang J, et al. Laquinimod arrests development of experimental autoimmune uveitis (EAU) and inhibits related immune processes, in the context of altered gut microbiota. Journal of Immunology. 2020; 204. 150.18
* Li Z, Chen J, Lei L, et al. Laquinimod inhibits inflammation-induced angiogenesis in the cornea. Front Med (Lausanne). 2020;7:598056

Safety profile of topical LAQ

- A phase 1 randomized, placebo-controlled, double-masked study in healthy participants demonstrated no clinically meaningful ocular or systemic adverse events

- Once daily up to 0.6mg LAQ vs. placebo for 21 days

* References: Placebo-Controlled, Double-masked Phase-1 Study in healthy subjects investigating the safety and tolerability of laquinimod eye drops. Clinical Trial NCT05187403.

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The LION study: safety, tolerability, and distribution of topical Laquinimod ophthalmic solution, an Innovative immunomodulatOr targeting aryl hydrocarboN receptor (AHR)

- 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)

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Key Inclusion Criteria

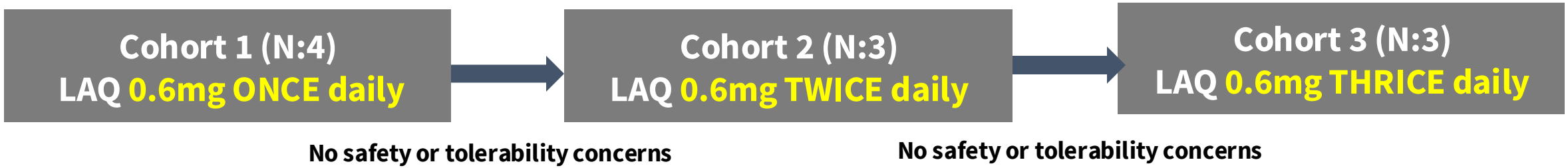
- Age: 18 years or older
- Scheduled to undergo **pars plana vitrectomy (PPV)**
- IOP ≥ 5 mmHg and ≤22 mmHg in the study eye

Key Exclusion Criteria

- Active periocular or ocular infectious disease
- Prior ocular surgery or intravitreal steroids within 90 days
- Intravitreal injection of anti-VEGF within 30 days
- Topical cyclosporine or corticosteroid or other specified (i.e. calcineurin inhibitors) within 2 weeks
- Strong inhibitors/inducers of CYP3A4 within 2 weeks
- Hepatic, renal or cardiac impairment

Methods

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



- LAQ concentration measured in the undiluted aqueous and vitreous humors as well as the plasma

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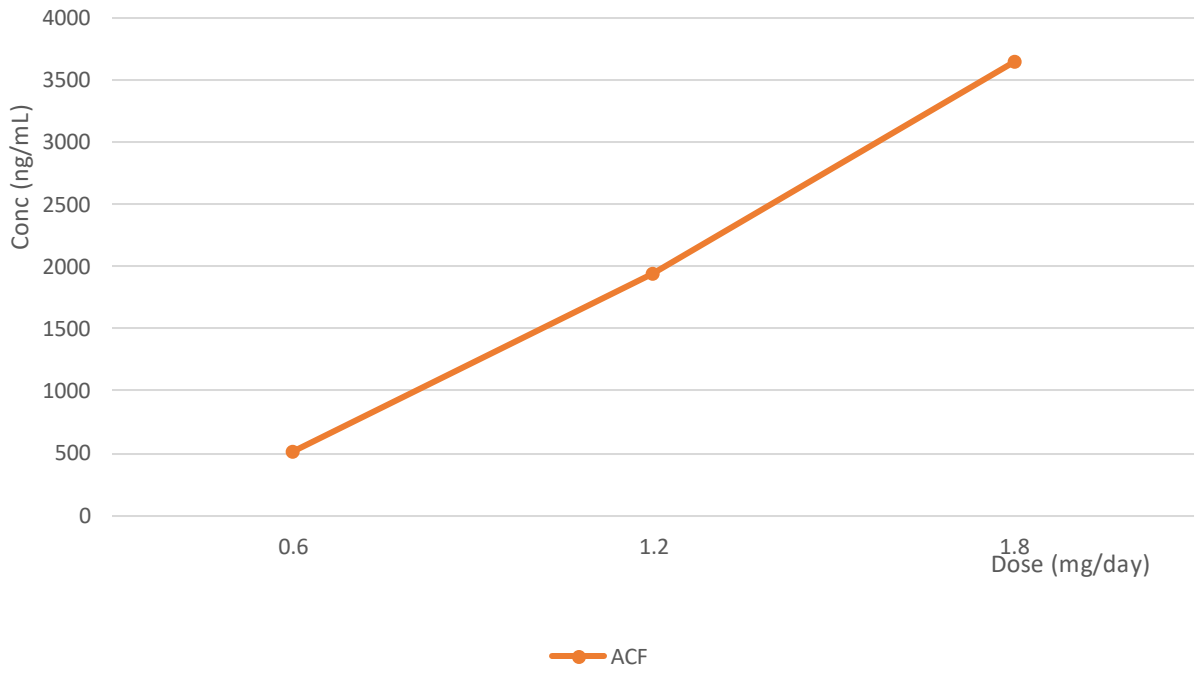
RESULTS

LAQ CONCENTRATION IN THE AQUEOUS

Cohorts (N:7)	Average LAQ Concentration (ng/ml)
Cohort 1 (N: 2) 0.6 mg	508.5
Cohort 2 (N: 3) 1.2 mg	1942.7
Cohort 3 (N: 2) 1.8 mg	3750



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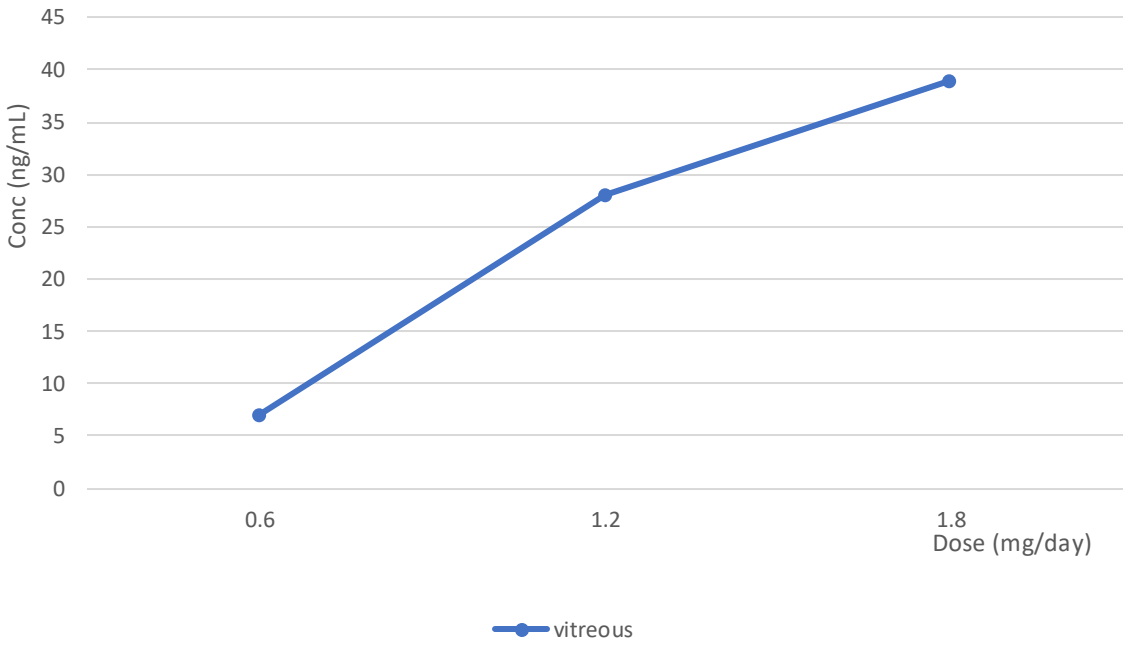
RESULTS

LAQ CONCENTRATION IN THE VITREOUS

Cohorts (N:8)	Average LAQ Concentration (ng/ml)
Cohort 1 (N: 2) 0.6 mg	6.9
Cohort 2 (N: 3) 1.2 mg	28.2
Cohort 3 (N: 3) 1.8 mg	41.3



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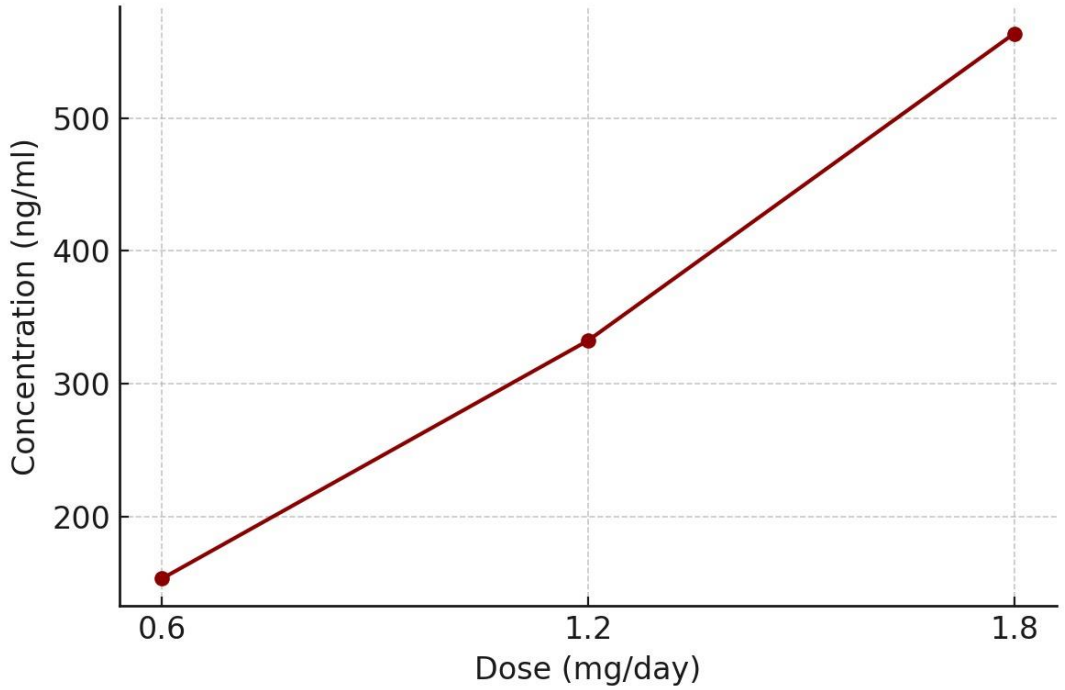
RESULTS

LAQ CONCENTRATION IN THE PLASMA

Cohorts (N:9)	Average LAQ Concentration (ng/ml)
Cohort 1 (N: 3) 0.6 mg	153.4
Cohort 2 (N: 3) 1.2 mg	332.5
Cohort 3 (N: 3) 1.8 mg	563.5



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LAQ CONCENTRATIONS IN AQUEOUS, VITREOUS AND PLASMA

Total Concentrations

Dose (mg/day)	**Aqueous** mean (nM)(SD)	**Vitreous** mean (nM) (SD)	**Plasma** mean (nM)(SD)
0.6	1425 (604)	19 (13)	427(33)
1.2	5445 (3470)	79 (73)	875(186)
1.8	10202 (9909)	108 (64)	1505(1072)

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

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Results
Safety Profile

- Topical LAQ was **well-tolerated** across **the three doses** without medication related-adverse events

  - ❑ BCVA
  - ❑ Ocular examination
  - ❑ Multimodal imaging (anterior, posterior SD-OCT and specular microscopy)
  - ❑ CBC
  - ❑ CMP
  - ❑ EKG

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Discussion

LION Cohorts (N:8)	Average LAQ Concentration in the vitreous (ng/ml)
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Cohort 3 (N: 3) 1.8 mg	41.3

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ORIGINAL ARTICLES

VITREOUS NONSTEROIDAL ANTIINFLAMMATORY DRUG CONCENTRATIONS AND PROSTAGLANDIN E_2 LEVELS IN VITRECTOMY PATIENTS TREATED WITH KETOROLAC 0.4%, BROMFENAC 0.09%, AND NEPAFENAC 0.1%

HEIER, JEFFREY S. MD*; AWH, CARL C. MD†; BUSBEE, BRANDON G. MD†; WATERBURY, L DAVID PhD‡; DANIEL, PAUL MS*; STOLLER, GLENN L. MD§; CLEARY, TINA S. MD*

Results:

Thirty-one patients were included in the analyses. The mean (SD) vitreous concentrations were as follows: ketorolac 2.8 (3.2) ng/mL, bromfenac 0.96 (0.31) ng/mL, nepafenac 1.1 (0.6) ng/mL, and amfenac 2.0 (0.8) ng/mL aligned with the initial concentrations of the topical NSAIDs. Mean (SD) vitreous prostaglandin E_2 levels of the control patients and those treated with ketorolac 0.4%, bromfenac 0.09%, or nepafenac 0.1% were 270.6 (91.7) pg/mL, 189.6 (50.2) pg/mL, 247.2 (38.3) pg/mL, and 267.7 (99.7) pg/mL, respectively. Patients treated with ketorolac 0.4% had significantly lower prostaglandin E_2 levels than those treated with no NSAID (P = 0.047) or nepafenac 0.1% (P = 0.028).

Conclusion:

All three NSAIDs penetrated into the vitreous cavity. Topical therapy with ketorolac may lower preoperative vitreous prostaglandin E_2 levels, which may have a clinical impact on the management of prostaglandin-mediated diseases, including cystoid macular edema.

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Discussion

Cohorts (N:8)	Average LAQ Concentration in the vitreous (ng/ml)
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Reduction of Vitreous Prostaglandin E_2 Levels After Topical Administration of Ketorolac 0.45%

Scott D. Schoenberger, MD[1]; Stephen J. Kim, MD[1]; Jinsong Sheng, MD[1]; et al

Objective To determine vitreous levels of ketorolac and prostaglandin E_2 (PGE_2) in eyes treated with topical ketorolac tromethamine 0.45% (Acuvail).

Design, Setting, and Participants A prospective comparative interventional study, performed in a university academic hospital, included 24 eyes in 22 consecutive patients undergoing pars plana vitrectomy.

Intervention Application of topical ketorolac 0.45%, 4 times daily, for 3 days before pars plana vitrectomy in the first 12 consecutive eyes. The next 12 eyes were untreated and served as controls. Undiluted vitreous samples were obtained at the time of surgery and immediately frozen at −80°C.

Main Outcomes and Measures Vitreous ketorolac and PGE_2 levels.

Results Seven of the 12 eyes (58%) had ketorolac levels above the lower limit of quantitation. All 7 were in pseudophakic eyes, and 4 of the 5 below this limit were phakic ($P = .01$). The mean ketorolac level in the 7 eyes was 7.55 ng/mL (range, 5.0-14.9 ng/mL). The mean (SD) PGE_2 levels were 13.8 (3.8) pg/mL in control eyes and 11.7 (4.4) pg/mL in ketorolac-treated eyes ($P = .04$). Treatment with ketorolac resulted in a 15% reduction in PGE_2 levels. When only pseudophakic eyes were analyzed, mean (SD) PGE_2 levels were 14.1 (4.1) pg/mL in control eyes and 11.6 (4.5) pg/mL in ketorolac-treated eyes ($P < .05$).

Conclusions and Relevance Topical ketorolac 0.45% can obtain a vitreous level that exceeds its median inhibitory concentration and can significantly decrease vitreous PGE_2 levels. Vitreous levels of ketorolac were significantly higher in pseudophakic eyes than in phakic eyes. The results of this study suggest that topically administered ketorolac 0.45% may allow meaningful inhibition of prostaglandins in the retina.

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Discussion

- The estimated **brain concentrations of free laquinimod** in MS patients on 0.6mg oral daily dose (effective dose): **10-20 nM**

Dose (mg/day)	**LAQ free Concentration in the Vitreous** mean (nM)
0.6	13
1.2	55
1.8	76

References: Varrin-Doyer M, Zamvil SS, Schulze-Topphoff U. "Laquinimod, an up-and-coming immunomodulatory agent for treatment of multiple sclerosis." Experimental Neurology (2014).

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, aqueous, and plasma

- The concentrations quantified in the vitreous are **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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Acknowledgments

This work would not have been possible without dedication, collaboration, and support of the entire team throughout the study

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