



# Laquinimod

- Treatment of inflammatory eye disorders

**Capital Markets Day**  
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# Laquinimod

## – Background

Mode of action	<ul style="list-style-type: none"><li>• Small molecule immunomodulator</li></ul>
Indication	<ul style="list-style-type: none"><li>• Inflammatory eye disorders</li></ul>
Clinical status	<ul style="list-style-type: none"><li>• Planning of phase 2 Proof-of-Principle study in uveitis, H2 2021</li></ul>
Safety	<ul style="list-style-type: none"><li>• &gt;5,000 persons exposed, &gt;14,000 person-years of exposure</li></ul>
Regulatory	<ul style="list-style-type: none"><li>• Regulatory package of preclinical and clinical safety</li></ul>
Drug supply	<ul style="list-style-type: none"><li>• Full commercial scale CMC documentation available</li></ul>
IP and exclusivity	<ul style="list-style-type: none"><li>• Protected by patents and patent applications to 2033</li><li>• Opportunity for orphan drug designation in uveitis</li></ul>

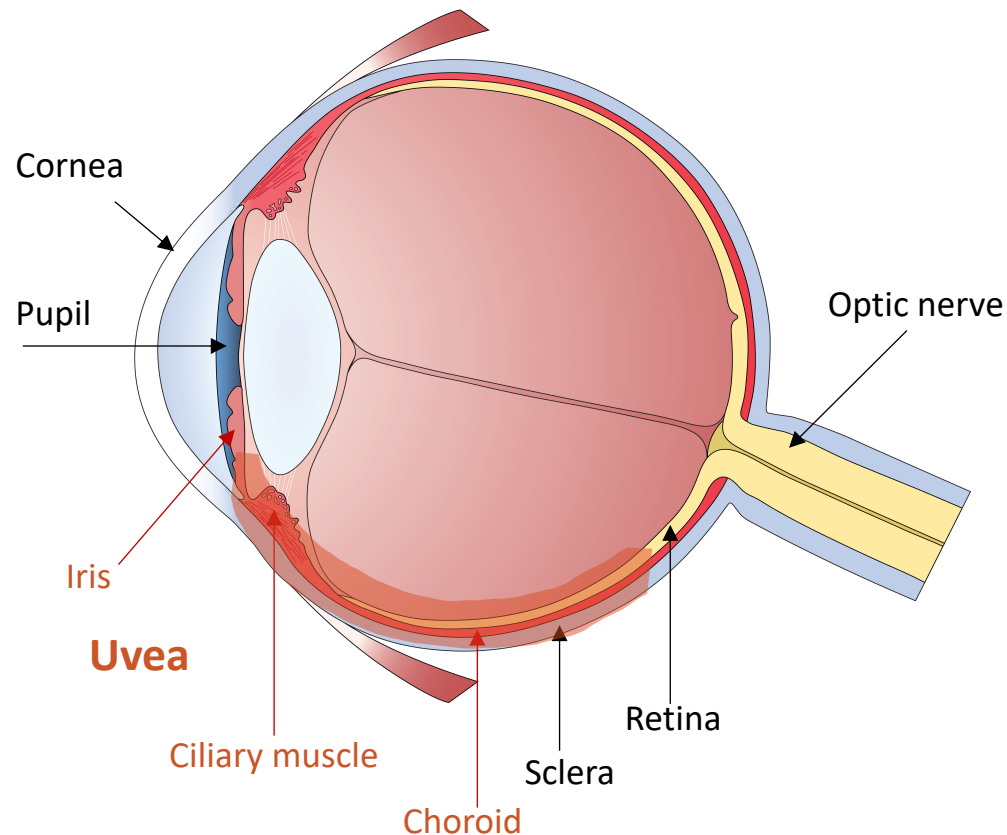


**Abbrev:** CMC - Chemistry, Manufacturing and Controls

# Uveitis

– A severe inflammatory eye disorders and the leading cause of blindness

Inflammation of the uveal tract with associated inflammation of the adjacent structures such as cornea, sclera, vitreous and retina



## Symptoms includes

- Decreased vision
- Dark floating spots
- Eye pain and redness
- Light sensitivity
- Swelling

## Cause of uveitis

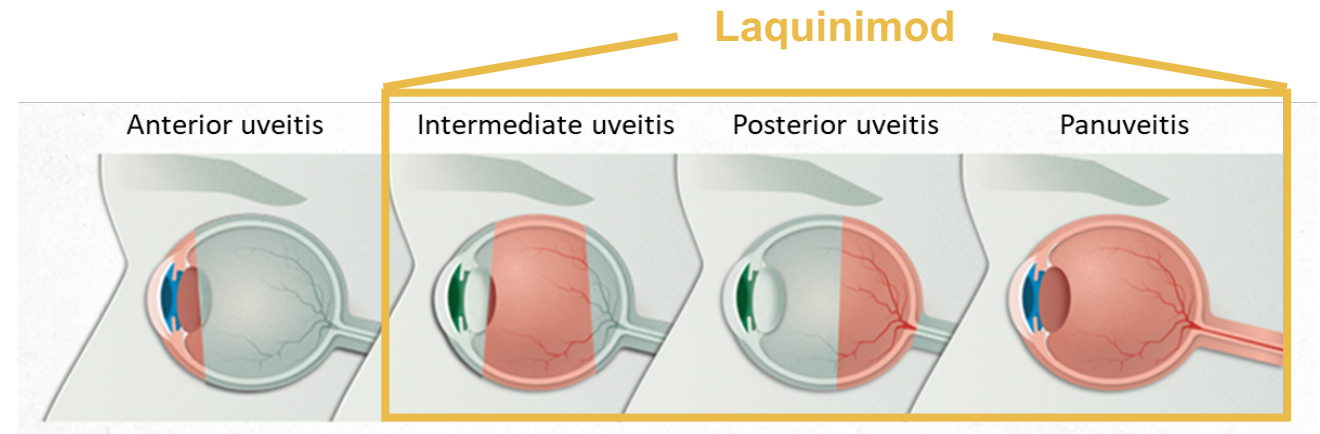
- Idiopathic
- Systemic autoimmune disease
- Infections
- Eye injury



# Uveitis

– Subtypes and today's treatments

- Infectious or non-infectious
  - Location of the inflammation
- Laquinimod will target non-infectious non-anterior uveitis



## Disease characteristics

- Affects mostly adults 20-60 yrs
- Vision loss most observed in non-anterior uveitis
- The third leading cause of blindness in the west world

## Today's treatment non-infectious non-anterior uveitis

### 1st Line of treatment

- Corticosteroids, oral, intravitreal or perocular injection

### 2nd and 3rd Line of treatment

- Immunosuppressants, oral
- Biologics – anti-TNF $\alpha$  antibodies (Humira®), subcutaneous

# Non-infectious non-anterior uveitis

## – Unmet medical need

- About 35 % of the patients suffer from severe visual impairment/blindness
- 40 % of the patients fail on steroid therapy
- Long-term treatment of steroids in high doses is associated with severe side effects
- No topical treatment options are available



### Unmet medical need

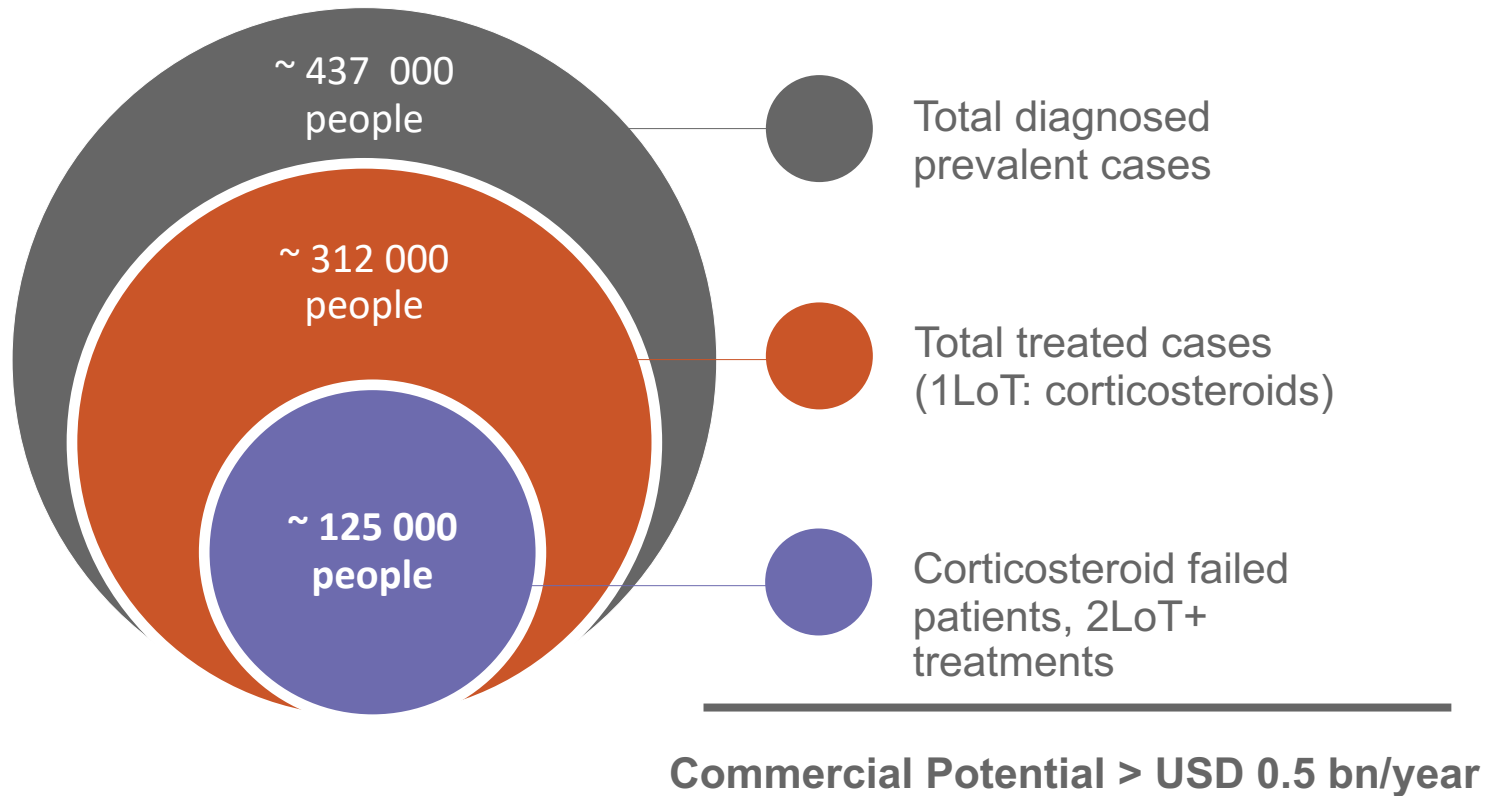
- A therapy with complimentary and additive efficacy to steroids, which limit proportion of 1<sup>st</sup>-line treatment failures
- A therapy that can reduce or possibly replace the need for long-term treatment with steroids to limit the systemic side effects related to high-dose steroid use
- A therapy which optimally is administered topically to minimize systemic side effects and reduction of injection-related risks



# Non-infectious non-anterior uveitis

– Addressable opportunity as an orphan indication

Significant opportunity in segment of non-infectious non-anterior uveitis in 7MM, forecasts for 2026



**Orphan disease in US and EU**  
**Corticosteroids only effective in 60%**  
**Clinical sequelae serious**



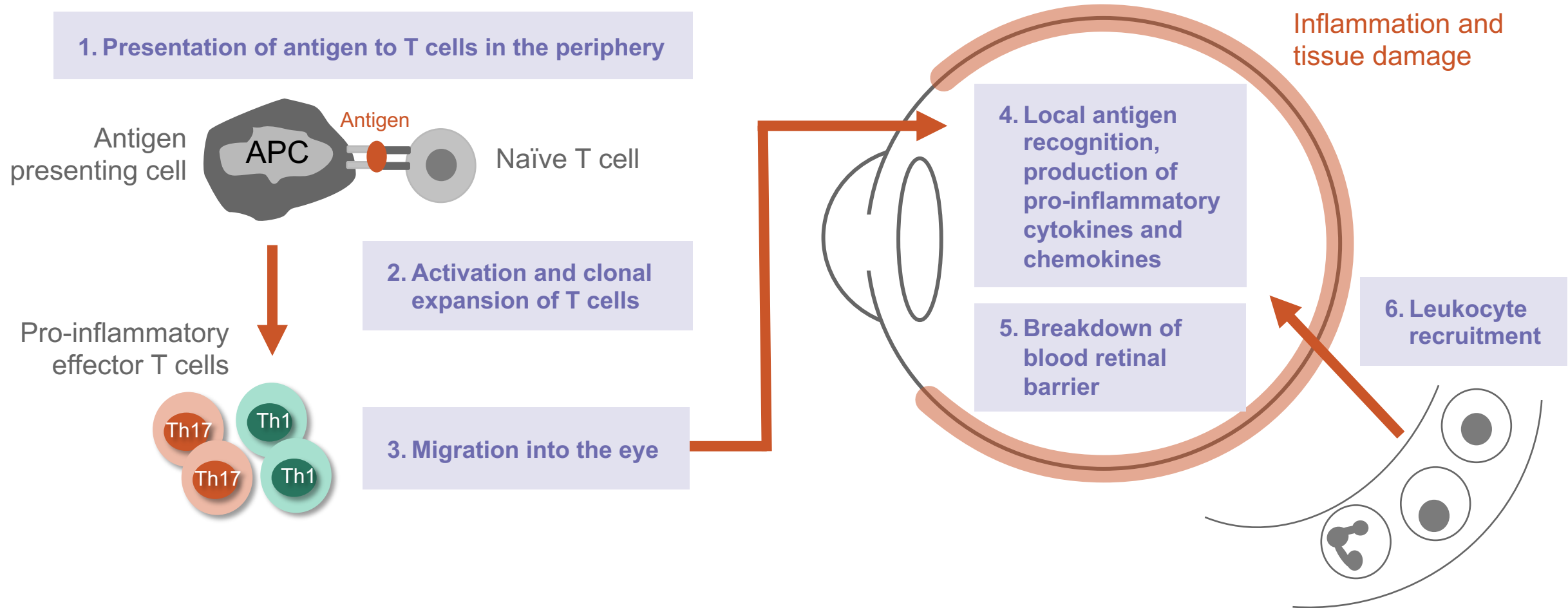
**Major unmet medical need**  
**Shortage of licensed therapies**  
**High cost of anti-TNF therapy**

**Abbrev:** LoT – Line of treatment

**Source:** GlobalData Oct 2017, 7 Major Markets (US, EU5, Japan). Presented data are based on 2026 forecast numbers.

# Non-infectious uveitis

## – Pathogenesis



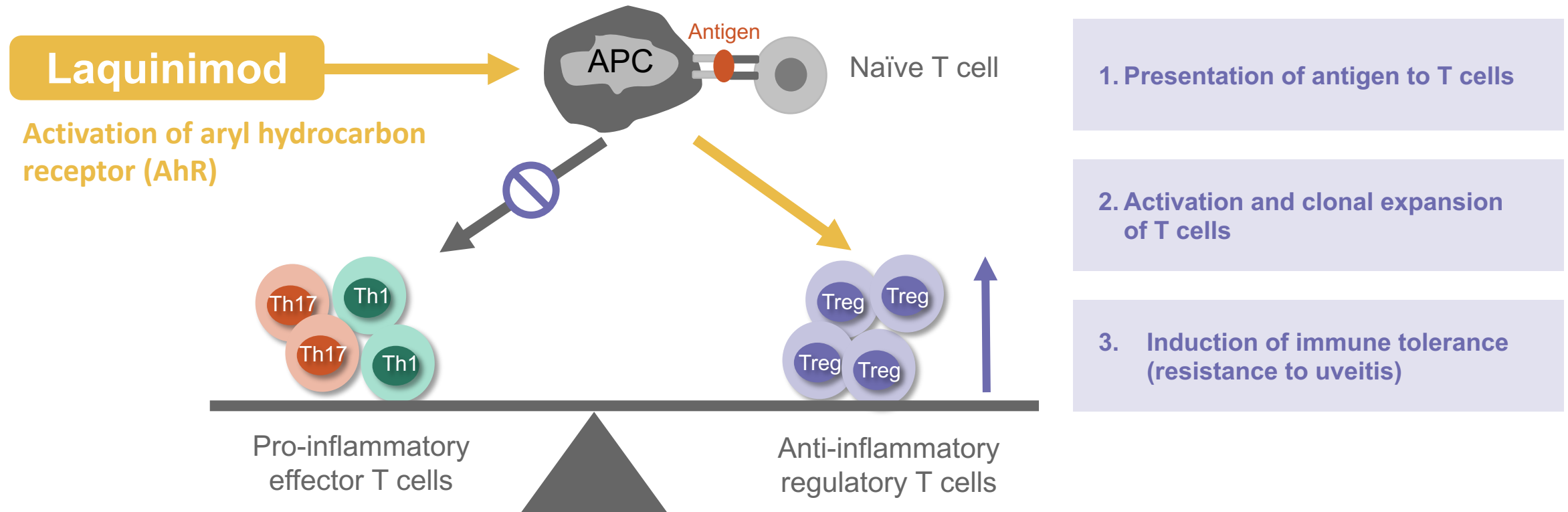
Abbr: APC- Antigen Presenting Cell, T reg-Regulatory T cell, Th 1-T helper cell 1, Th17-T helper cell 17



# Laquinimod

## – Mode-of-action

Laquinimod skews antigen presenting cells towards an anti-inflammatory phenotype, resulting in reduction of pro-inflammatory T cells and increase of anti-inflammatory regulatory T cells

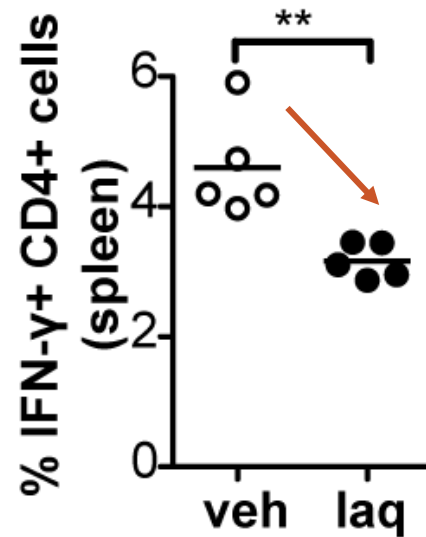


**Abbr:** AhR – Aryl hydrocarbon Receptor, APC- Antigen Presenting Cell, T reg-Regulatory T cell, Th 1-T helper cell 1, Th17-T helper cell 17

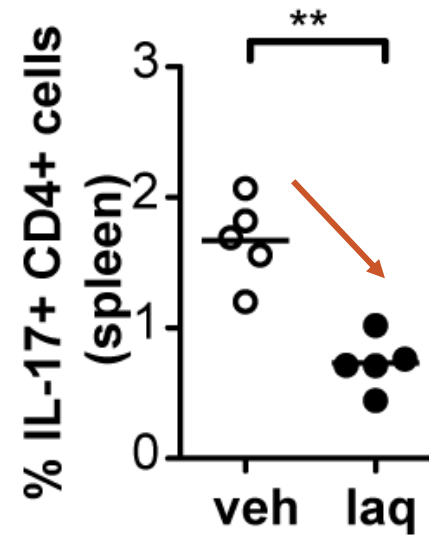
# Laquinimod

– Shift of balance from pro-inflammatory T cells to anti-inflammatory regulatory T cells

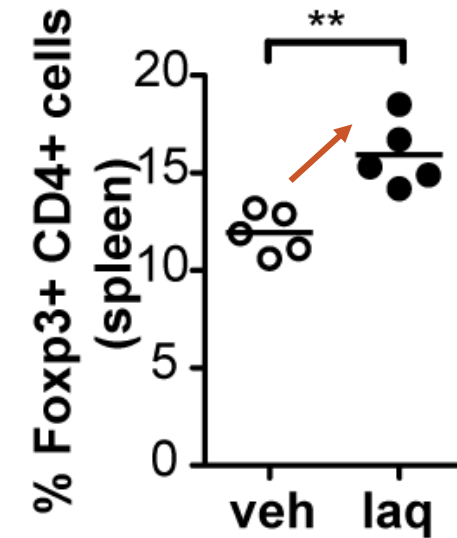
Th1 cells



Th17 cells



Treg cells



**Abbr:** veh – Vehicle, laq - laquinimod, IFN- $\gamma$  – interferon-gamma, IL – interleukin, CD – cluster of differentiation, Foxp3 – forkhead box P3, T reg-Regulatory T cell, Th 1-T helper cell 1, Th17-T helper cell 17, Treg – regulatory T cells.

**Reference:** Shulze-Toppoff et al. PLOS One, 2012;7(3)

# Laquinimod

– Oral administered laquinimod is a potent inhibitor of experimental uveitis



**Laquinimod arrests development of experimental autoimmune uveitis (EAU) and inhibits related immune processes, in the context of altered gut microbiota**

Biying Xu, Xiuzhi Jia, Jihong Tang, Rachel R Caspi and Igal Gery  
J Immunol May 1, 2020, 204 (1 Supplement) 150.18, Published

## Abstract

### Study design

Experimental autoimmune uveitis (EAU) model in C57BL/6J mice. Immunization with the uveitogenic antigen, IRBP 651–670. Oral laquinimod treatment from day 0 or day 7, relative to immunization, Disease progression was monitored by ocular fundus examination and confirmed by histology day 19.

### Results

Start of treatment with laquinimod day 0 or day 7 showed:

- **Clear reduction of clinical manifestation of uveitis**
- **Reduction of pro-inflammatory T cells and cytokines**
- **Increased of anti-inflammatory regulatory T cells**

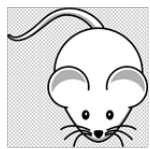
Study performed in collaboration with Dr Rachel Caspi, Dr Igal Gery and Biying Xu at NIH/National Eye Institute (NEI), Maryland (Manuscript in preparation)

**Abbrev.** EAU- Experimental Autoimmune Uveitis, IRBP – Interphotoreceptor Retinoid Binding Protein;

# Laquinimod

– Topical administration of laquinimod reduces clinical manifestation of experimental uveitis

## Experimental acute uveitis (EAU)



Lewis rat  
(albino)

**Day 0:** Immunization with 100 µg retina specific S-antigen in CFA

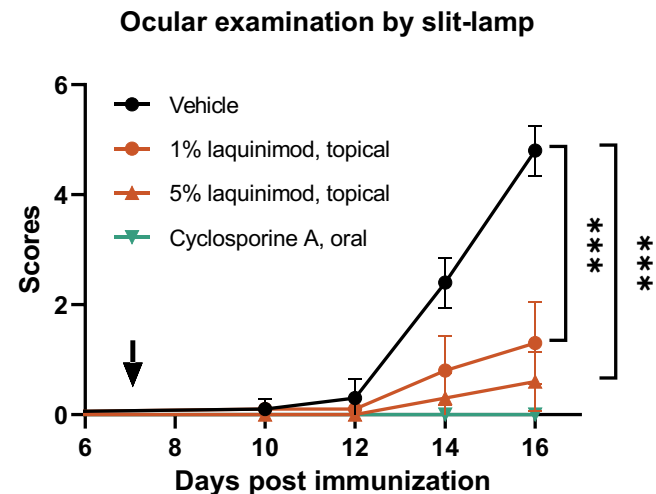
**Day 7-16:** Laquinimod,  
1% or 5% solution, topical

**Day 7-16:** Cyclosporine A;  
25 mg/kg/day, oral

### Quantification of disease

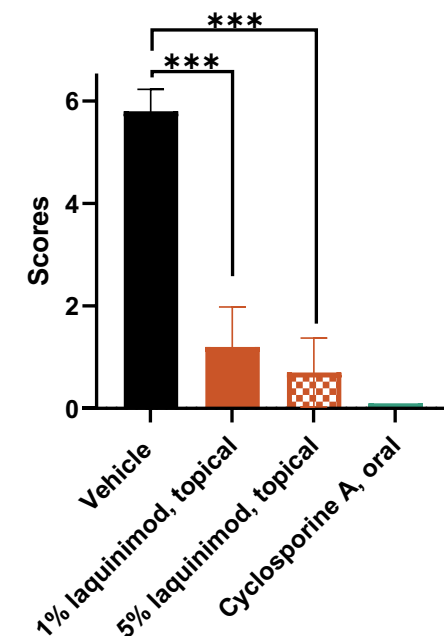
- Ocular examination by slit-lamp, day 10-16
- Histological ocular evaluation, day 16

## Decreased inflammation in the anterior part of the eyes



## Decreased inflammation in the posterior part of the eye

### Histological ocular evaluation



**Abbrev.** EAU- Experimental Autoimmune Uveitis, CFA - Complete Freund's Adjuvant



# Laquinimod development program for Uveitis

– Advancing the clinical program using existing capsule formulation

- Full commercial scale CMC documentation available
- Safety data from > 5,000 exposed persons
- Full IND regulatory documentation available
- Substantial pre-clinical proof-of-principle
- Laquinimod is clinical phase 2 ready
  - Preparation for study start



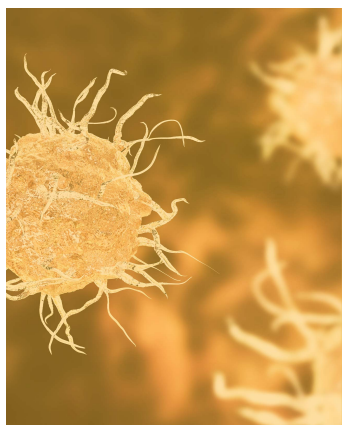
- Topical formulation, for use with or instead of capsules, developed in collaboration with Leukocare AG
- Available IND regulatory package is being completed with pre-clinical local tolerance study
- Clinical phase 1 safety study ahead of clinical efficacy trial
  - Preparation for study start



**Abbrev.** CMC - Chemistry, Manufacturing and Controls, IND - Investigational New Drug

# Laquinimod – activities through 2023

LAQUINIMOD

	2020	2021 H1	2021 H2	2022 H1	2022 H2	2023
	<ul style="list-style-type: none"> <li>✓ Partnership with Leukocare AG established</li> <li>✓ Development of new topical eye formulation</li> <li>• Translational studies - ongoing</li> </ul>	<ul style="list-style-type: none"> <li>• Preclinical local tolerance</li> <li>• Manufacturing of clinical material</li> <li>• Announcement of academic partnership</li> </ul>	<p><u>Ph2-oral:</u> <b>Start</b></p> <p><u>Ph1- topical</u> <b>Start</b></p>		<p><u>Ph1-topical</u> <b>Readout</b> safety</p>	<p><u>Ph2-oral</u> <b>Readout</b> proof-of-principle</p>

## Preclinical/CMC program

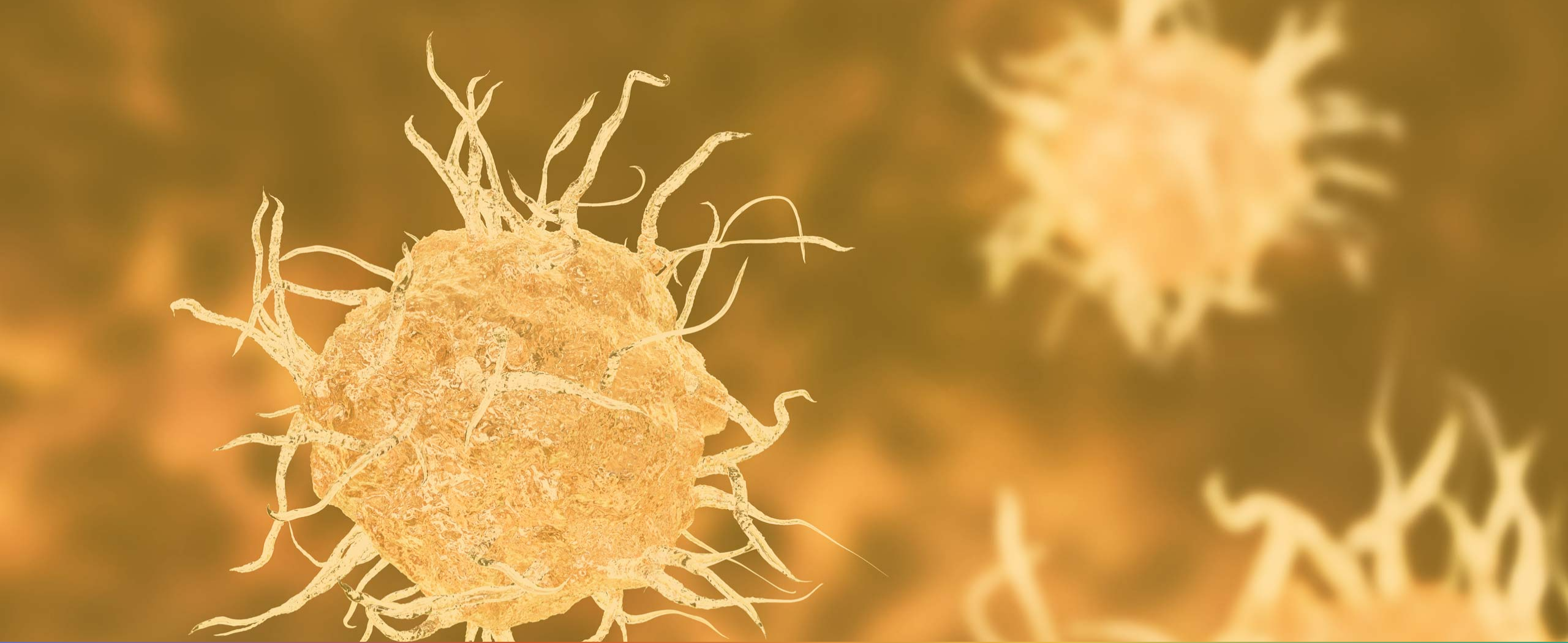
- ✓ Development of topical formulation - done
- Translational studies in *in vitro* and *in vivo* models - ongoing
- Preclinical - local tolerance of topical eye formulation, H1 2021
- Manufacture of topical eye formulation for clinical trials, H1 2021
- Manufacture of capsules for planned clinical trials, H1 2021

## Clinical development program

- Prepare for clinical phase 1 study of topical eye formulation, start in H2 2021
- Prepare for proof-of-principle phase 2 study (oral), start in H2 2021

**Abbrev:** CMC - Chemistry, Manufacturing and Controls

Ongoing and planned clinical trials may be affected by COVID-19. We will provide updates as needed.



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