2017 Research and Development Day

October 10, 2017

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Aldeyra Therapeutics
2017 Research and Development Day

New Results from Phase 2 Clinical Trials in Allergic Conjunctivitis and Dry Eye Disease

- David Clark, MD, Chief Medical Officer, Aldeyra

Unmet Medical Need in Allergic Conjunctivitis and Dry Eye Disease

- Tim Surgenor, RedSky Partners, LLC

Clinical and Regulatory Opportunities in Dry Eye Disease

- Gary Novack, PhD, Visiting Professor of Pharmacology and Ophthalmology, University of California, Davis, School of Medicine

The Intersection of Dry Eye Disease and Allergic Conjunctivitis

- John Sheppard, MD, Professor of Ophthalmology at Eastern Virginia Medical School

Introduction of ADX-103 and the Retinal Disease Program

- Susan Macdonald, PhD, Vice President of Research and Development, Aldeyra

Clinically Important Response Results from Phase 2b Clinical Trial in Allergic Conjunctivitis

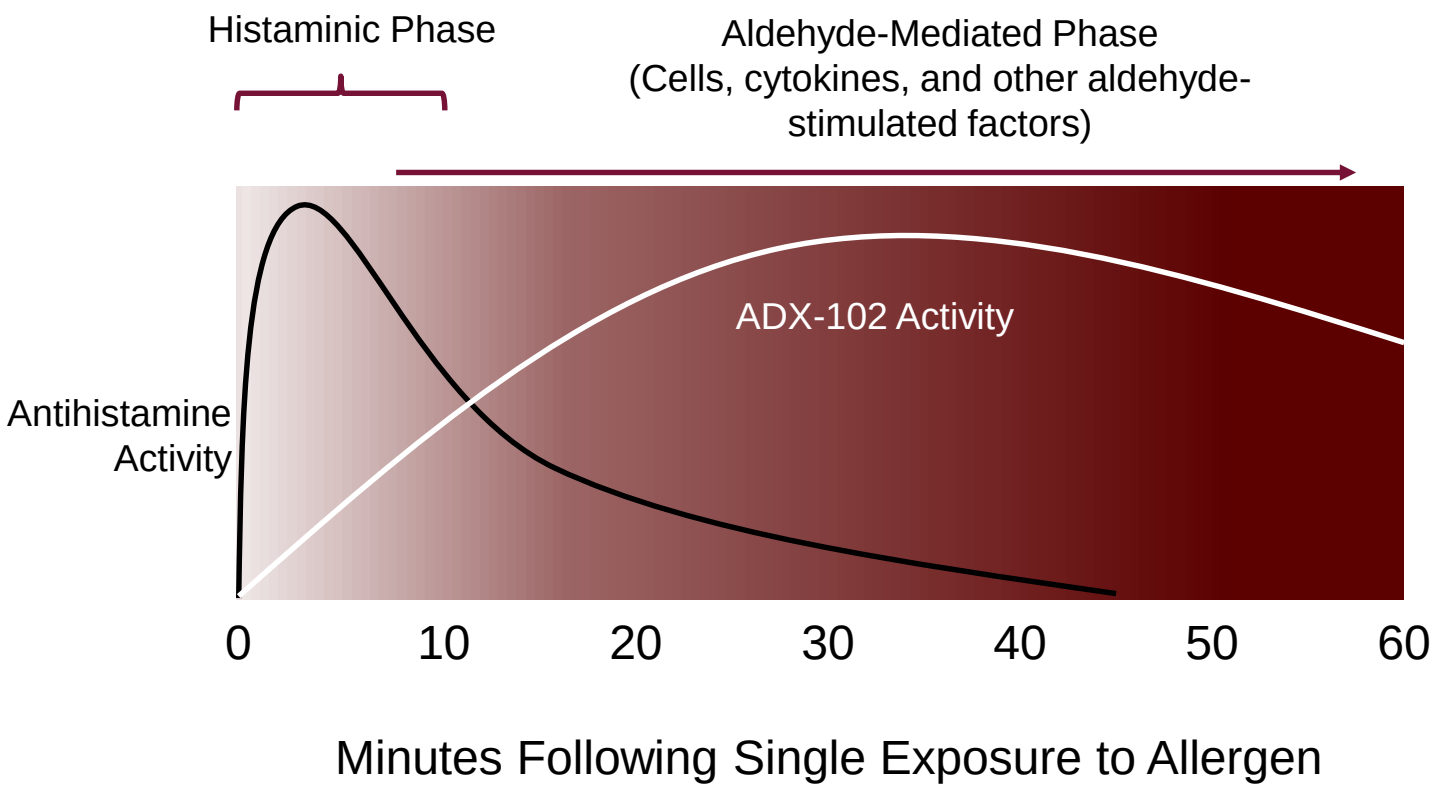
David Clark, MD
Chief Medical Officer
Aldeyra Therapeutics

Allergic Conjunctivitis Phase 2b Clinical Design

Groups	Topical Ocular ADX-102 0.1%, ADX-102 0.5%, or Vehicle
Randomization	Double-Masked, Vehicle-Controlled 1:1:1
Enrollment	154 Patients with History of Allergic Conjunctivitis
Model	Single Dose Seasonal and Perennial Allergen Challenge
Endpoint	Patient-Reported Itching Score (0 to 4)

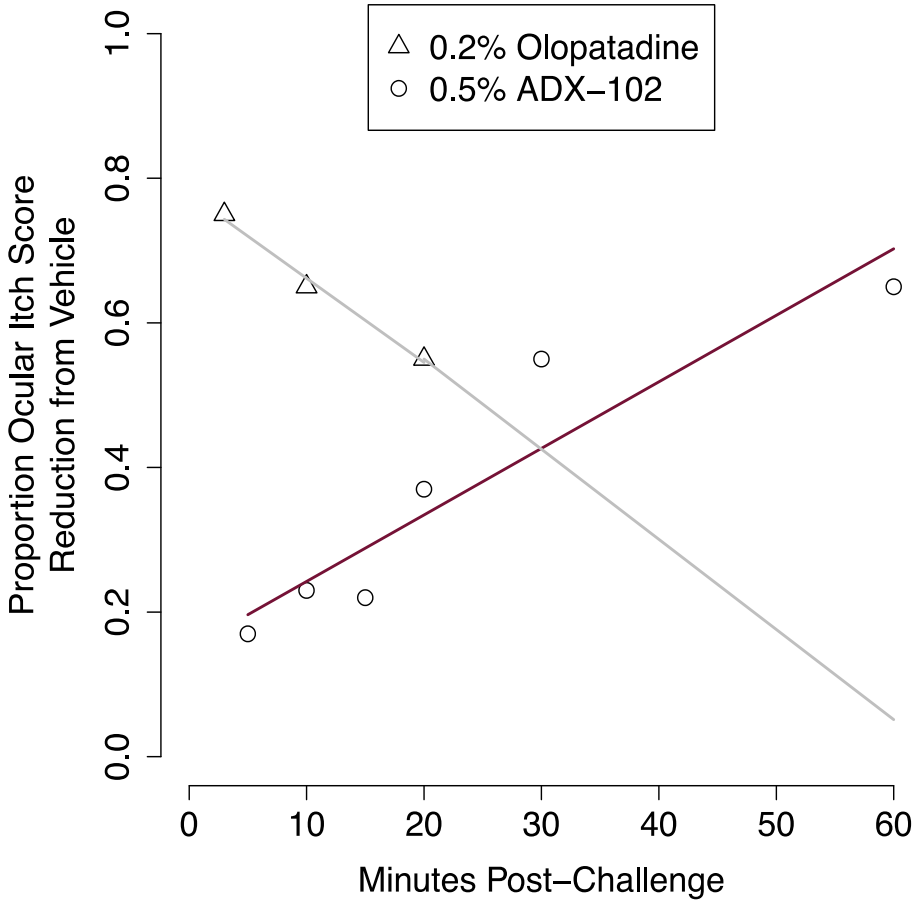
Further information can be found on www.clinicaltrials.gov: Trial #NCT03012165.

Histaminic and Aldehyde-Mediated Phases After Allergen Challenge



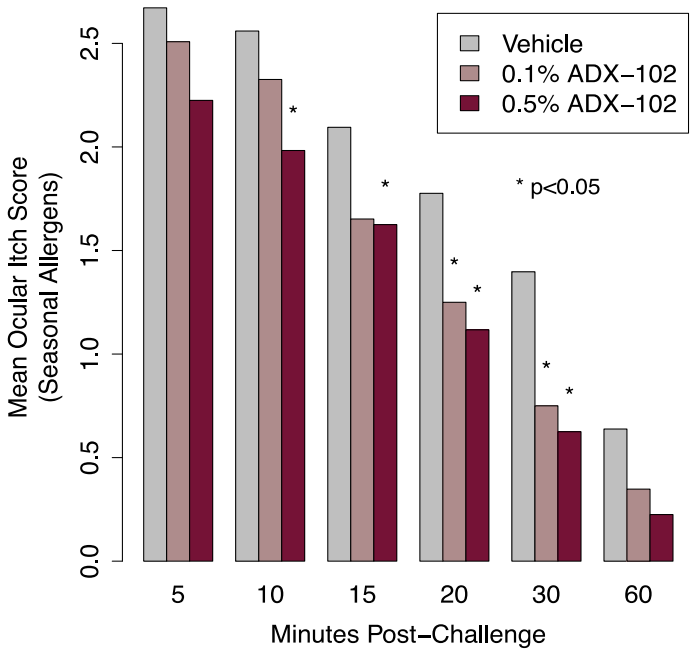
In Phase 2 clinical trials, ADX-102 shown to be effective for aldehyde-mediated allergy, for which no drug is approved, and which affects all allergic conjunctivitis patients.

The Activity of Antihistamines Diminishes Rapidly as ADX-102 Activity Increases



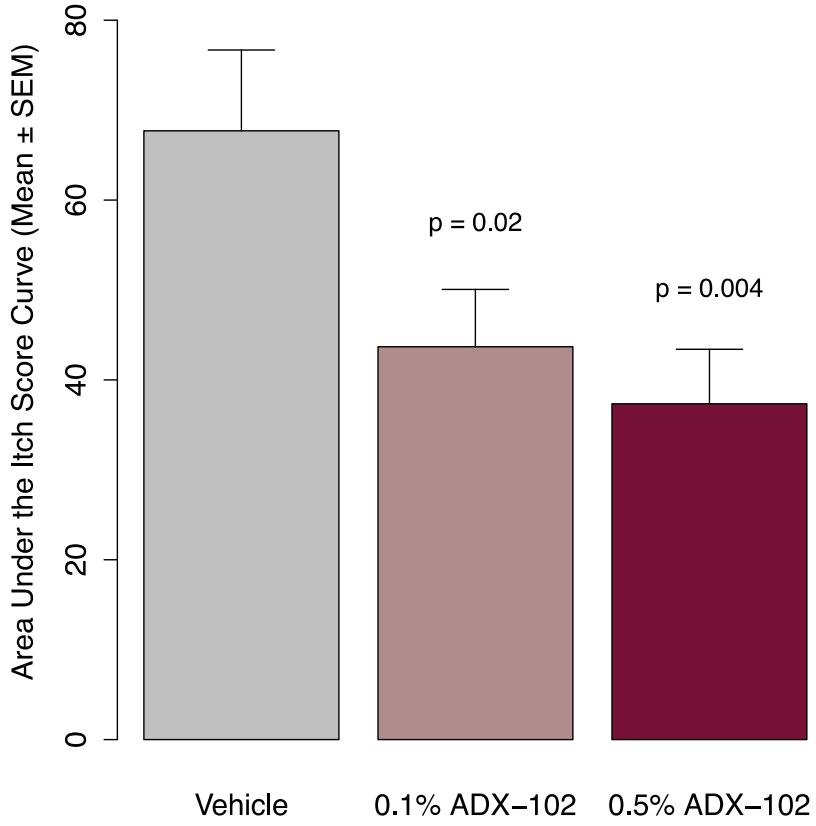
Data from olopatadine Summary Basis of Approval, ADX-102 Phase 2b clinical trial.

ADX-102 Decreased Ocular Itch in Phase 2b Clinical Trial



ADX-102 was statistically superior to control in reducing allergic ocular itch 10 to 60 minutes after allergen challenge, when the activity of antihistamines diminishes.

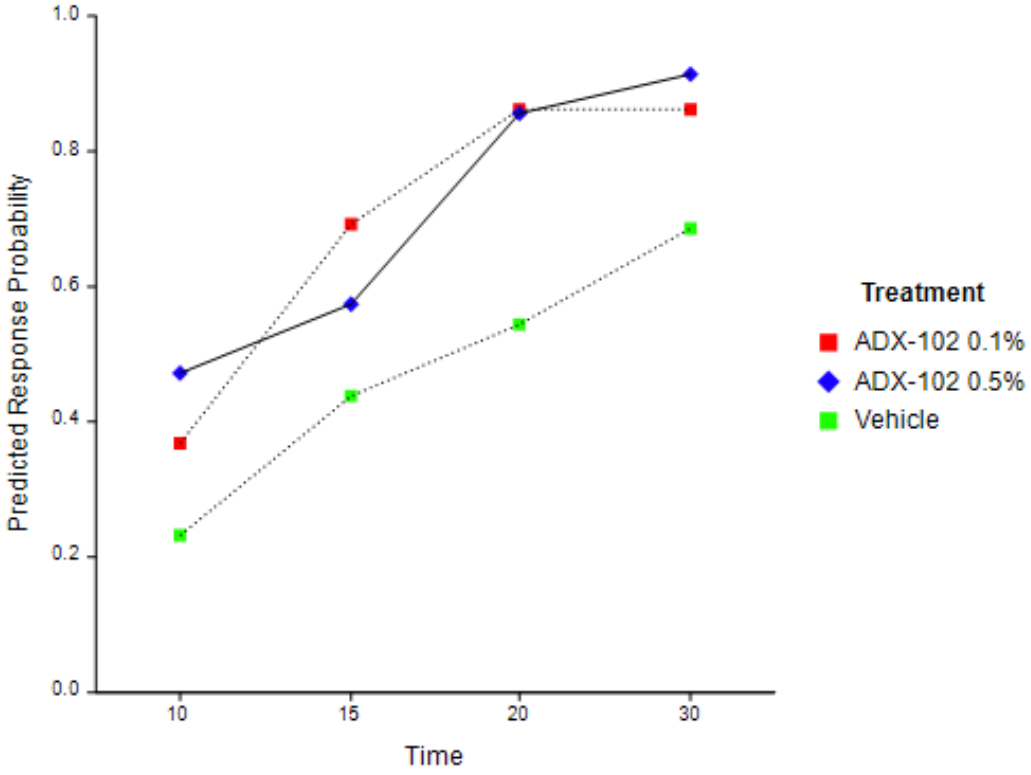
ADX-102 Decreased Area Under the Curve Ocular Itch Score in Phase 2b Clinical Trial



Area under the curve indicated a durable effect of ADX-102 in reducing ocular itch score in a manner that is statistically superior to that of control 10 to 60 minutes after allergen challenge, when the activity of antihistamines diminishes.

Probability of Clinically Important Response Was Statistically Higher in ADX-102-Treated Patients

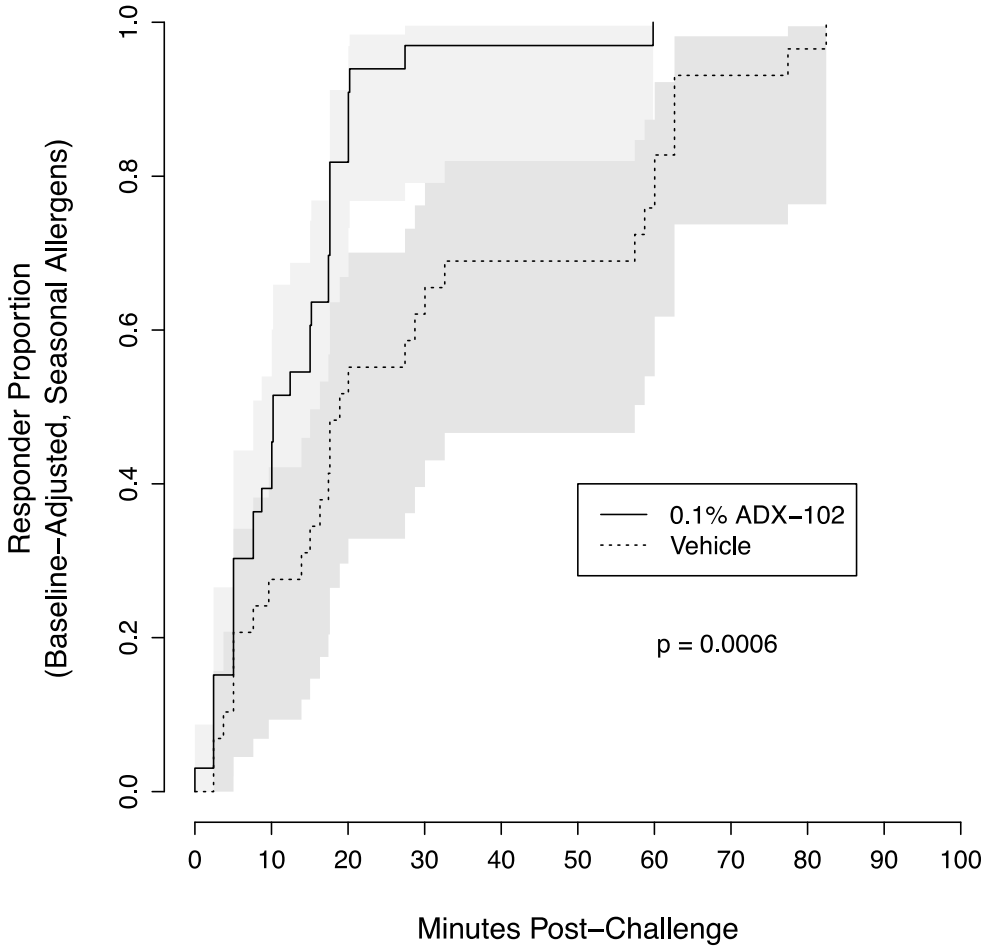
- One-point improvement in ocular itch score is US FDA regulatory precedent
- When a responder is defined as a patient that improves one point from peak baseline itch score, odds ratio analysis indicated that ADX-102-treated patients were more than three times as likely to achieve clinical response (p=0.02 for each drug group) in the Phase 2b clinical trial



Data from ADX-102 Phase 2b clinical trial.

Clinical Response Achieved Faster in ADX-102 Group vs. the Vehicle Group

- 0.1% and 0.5% ADX-102 groups achieved statistically faster clinical response than vehicle (p=0.0006 and p=0.008, respectively).
- As an example, the graph to the right indicates that 94% of 0.1% ADX-102-treated patients responded by 20 minutes post-challenge in the Phase 2a clinical trial.



p values are subject to change based on quality control analysis. Data from ADX-102 Phase 2b clinical trial.

Allergic Conjunctivitis Phase 2b Key Conclusions

- ADX-102 was shown to be statistically superior to vehicle in durably reducing ocular itch score from 10 to 60 minutes after exposure to allergen, an efficacy profile that has not been demonstrated for antihistamines.
- Relative to control, the activity of ADX-102 increased during a period when the activity of antihistamines decreases.
- Using the US FDA regulatory precedent of one point improvement on the ocular itch score, the clinical response of drug-treated patients was statistically superior to that of vehicle treated patients, when response is measured vs. peak baseline itch score.
- Using odds ratio analysis, ADX-102-treated patients were more than three times more likely to respond than vehicle-treated patients.
- Time to response was statistically faster in ADX-102 treated patients vs. that of vehicle-treated patients.

Allergic Conjunctivitis Phase 3 Clinical Design

Groups	Topical Ocular ADX-102 0.1%, ADX-102 0.5%, or Vehicle
Randomization	Double-Masked, Vehicle-Controlled 1:1:1
Enrollment	150 Patients with History of Allergic Conjunctivitis
Model	Single Dose Seasonal Allergen Challenge
Endpoint	Patient-Reported Itching Score (0 to 4)

*Pending additional non-clinical data and other factors, which may not be in Aldeyra's control

A Market-Based Analysis of Unmet Medical Need in Allergic Conjunctivitis and Dry Eye Disease

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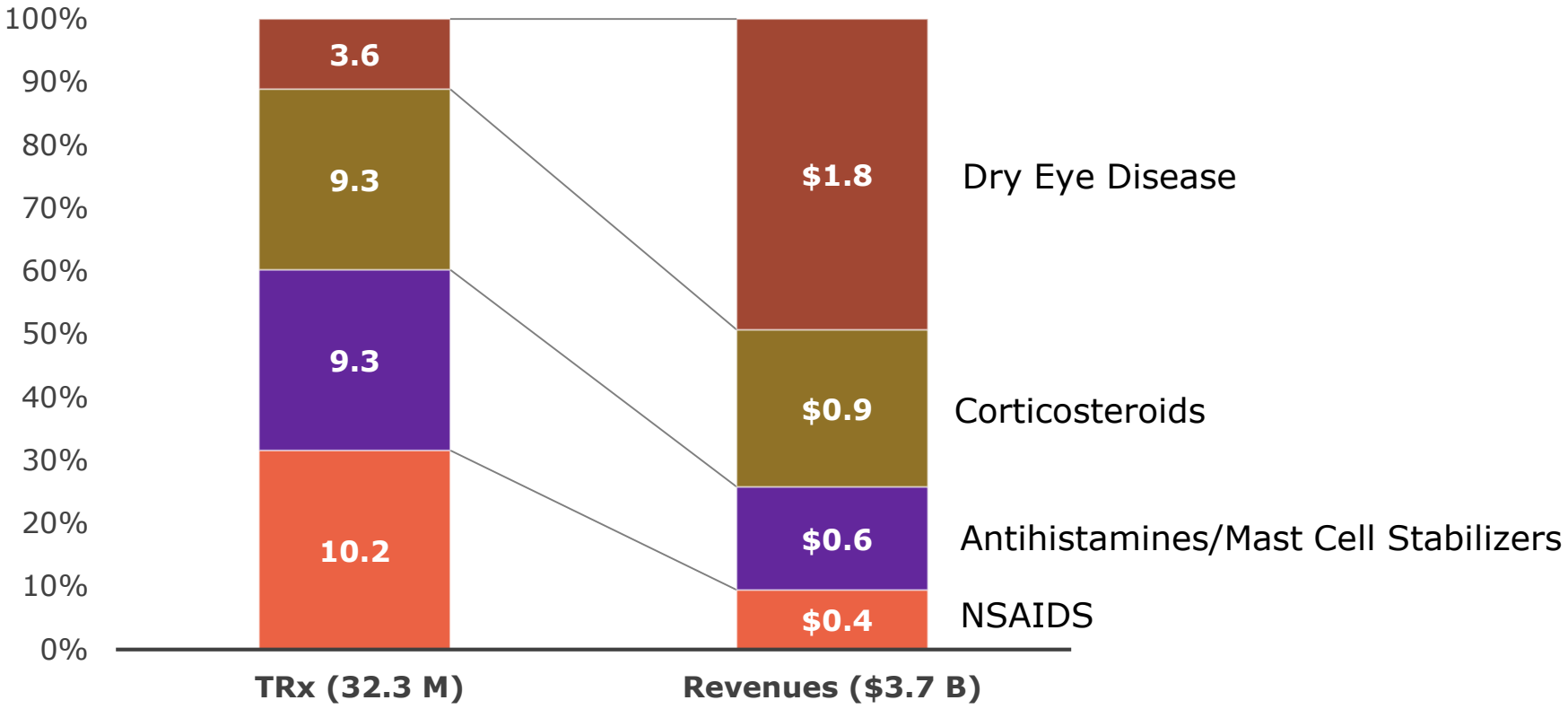
The opinions expressed herein are those of RedSky Partners, LLC and do not necessarily reflect the views of Aldeyra.

Overview

- ADX-102, if approved, has potential to be differentiated, branded entry in market for eye drop treatments
- ADX-102 appears to provide clinically significant improvement in phase 2 studies in multiple indications
  - allergic conjunctivitis
  - dry eye disease
  - noninfectious anterior uveitis
- Positioning as first line anti-inflammatory with unique mechanism and without steroid adverse events may convey significant market potential in anterior uveitis and dry eye disease
- In allergic conjunctivitis, positioning between short-acting antihistamines and corticosteroids is differentiated and attractive to physicians

US Eye Drop Market in 2016



Source: IMS

Emerging Value Proposition – ADX-102

	Noninfectious Anterior Uveitis	Dry Eye	Allergic Conjunctivitis
Market Need	• ~150,000 US patients • Treated with corticosteroids, which may lead to cataracts and glaucoma	• ~20 million patients • Only two approved drugs • Therapy generally considered to be inadequate	• ~20% of US population • ~60 million patients • Antihistamines provide short term relief • Off-label use of chronic corticosteroids represents safety risk
ADX-102 Efficacy Profile	• Efficacy similar to corticosteroid monotherapy at 4 weeks in Phase 2b trial	• Statistically significant improvement in multiple signs and symptoms at 4 weeks, with apparent rapid onset in Phase 2a trial	• Statistically significant reduction in itching at 10-60 minutes after challenge in Phase 2b trial
Safety / Tolerability to Date	• No observed increase in intraocular pressure • No observed significant adverse events	• Favorable tolerability • No observed significant adverse events	• Favorable tolerability • No observed significant adverse events
Dose being studied	0.5%	0.1%, 0.25%	0.1%, 0.5%

- Opportunity for lifecycle management and dose form opportunities

Source: ALDX press releases

ADX-102 Opportunity in Allergic Conjunctivitis

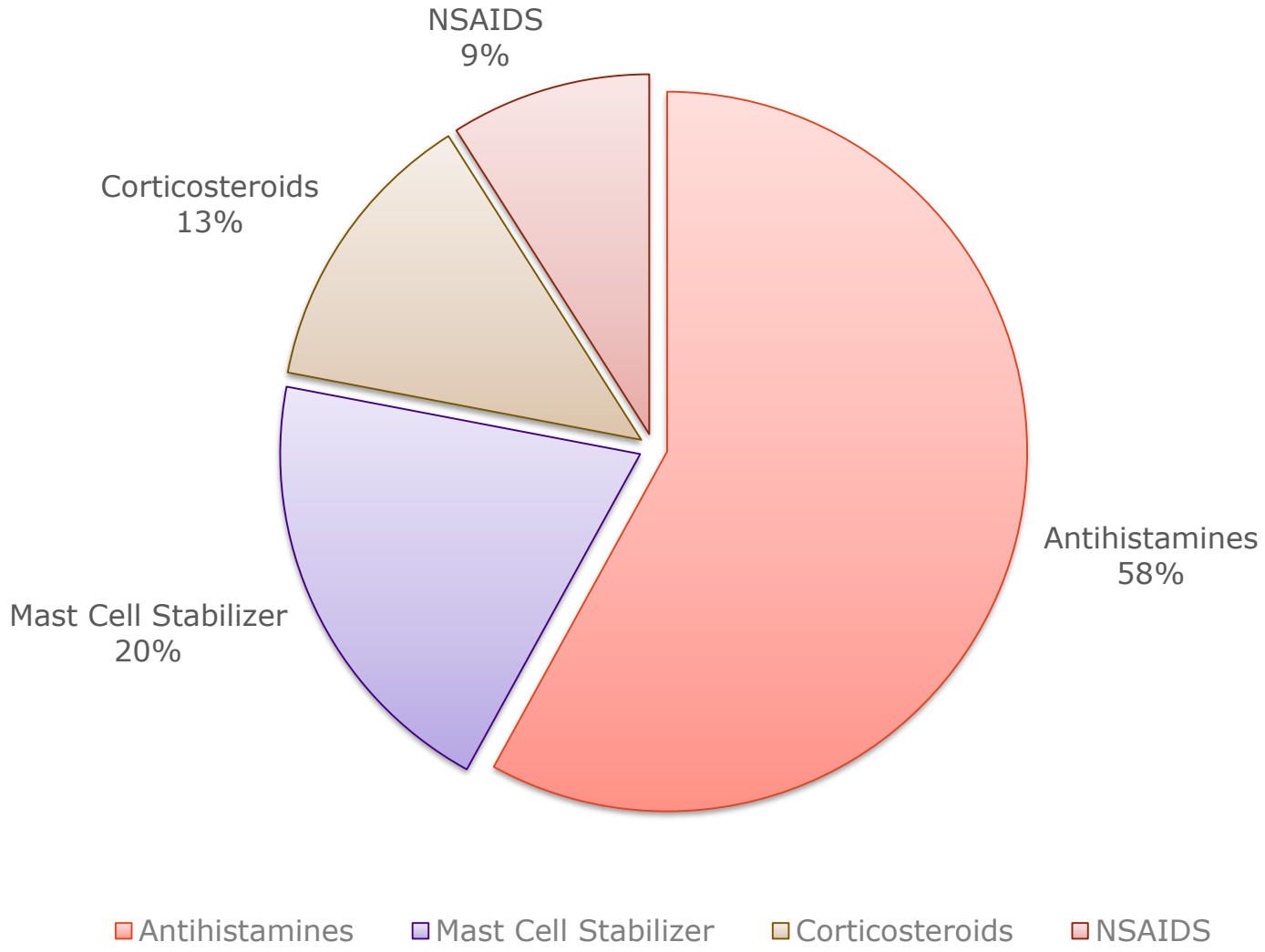
- Allergic conjunctivitis – inflammatory disease of conjunctiva resulting from allergen exposure
- Affects ~20% of US population with range of severity
- Mast-cell stabilizers or antihistamines provide short term relief –acute phase allergic reaction (up to 20 minutes)
  - Histamine release is acute; antihistamines work immediately following allergen exposure
  - Activity of antihistamines diminishes rapidly
- Patients with chronic or severe forms of allergic conjunctivitis are treated with topical corticosteroids – creating long-term risks of cataracts and glaucoma
- ADX-102 Hypothesis
  - Aldehyde trap mechanism could be substantial market opportunity for patients with inadequate relief from antihistamines and who are not candidates for corticosteroids

Survey Overview

- Survey of 75 US Physicians
  - Ophthalmology - 45
  - Optometry - 15
  - Allergy / Immunology - 15
- Conducted in July 2017 on behalf of Aldeyra
- Active in treatment of allergic conjunctivitis

Source: GLG market research

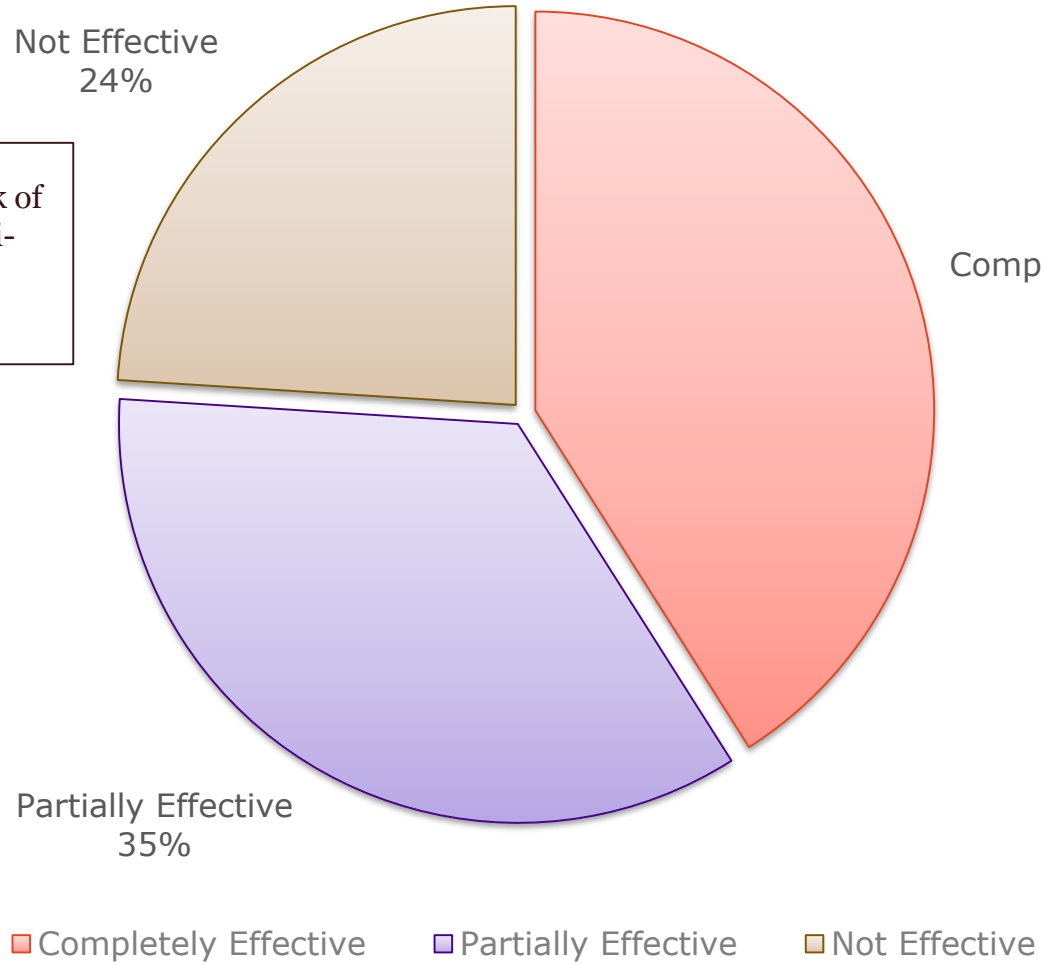
How do you currently treat your AC patients with topical products?



Source: GLG market research

For AC patients treated with topical ophthalmic antihistamines, what percent apply to each category below?

36% of patients with lack of sustained relief on anti-histamines switch to corticosteroids



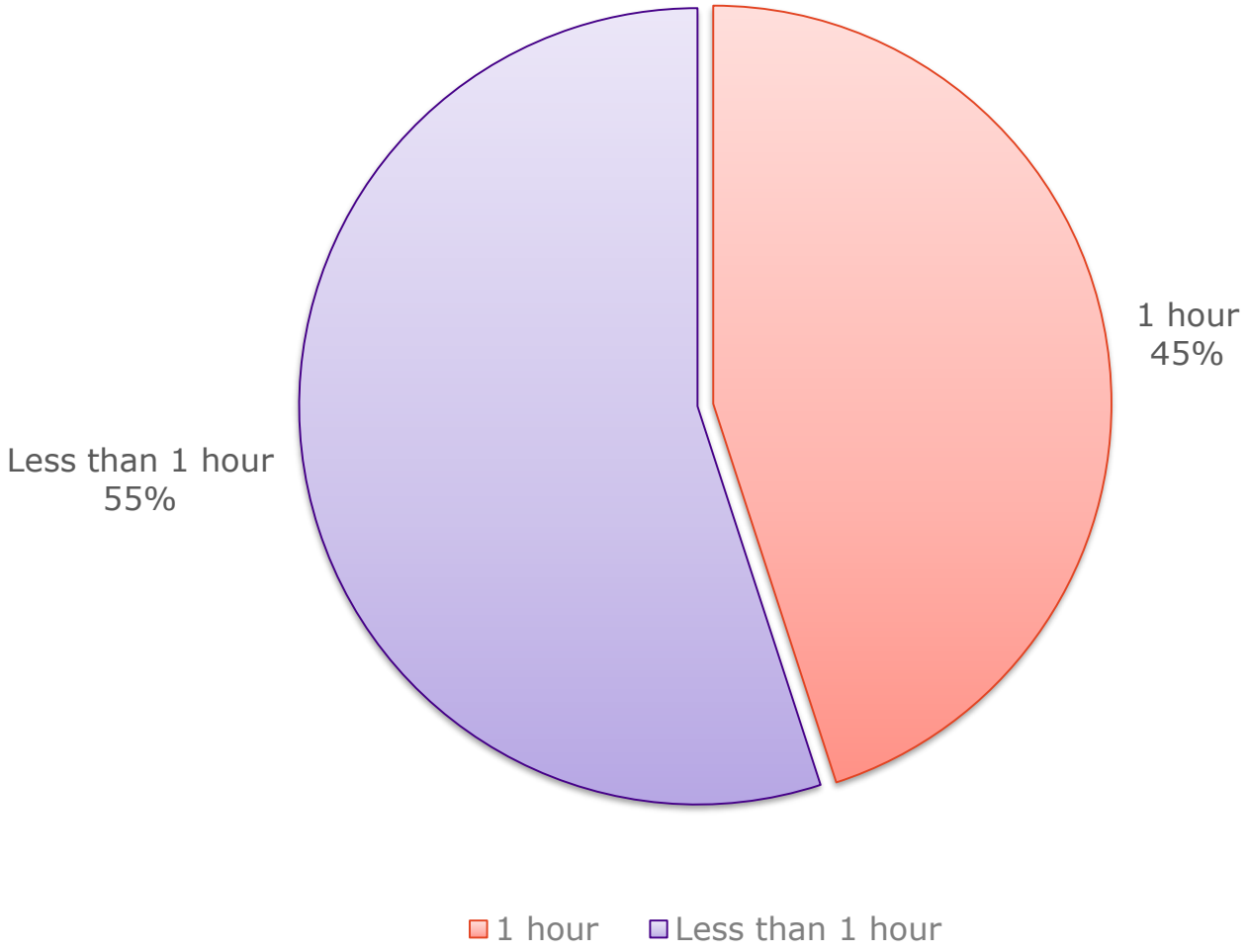
Source: GLG market research

Cross-sectional study of allergic conjunctivitis consistent with survey results

- 2015 Study in Italy
- 2687 Allergic conjunctivitis patients
  - 43% used OTC
  - 29% used topical antihistamines
  - 41% used corticosteroids
  - 60% used multiple medications

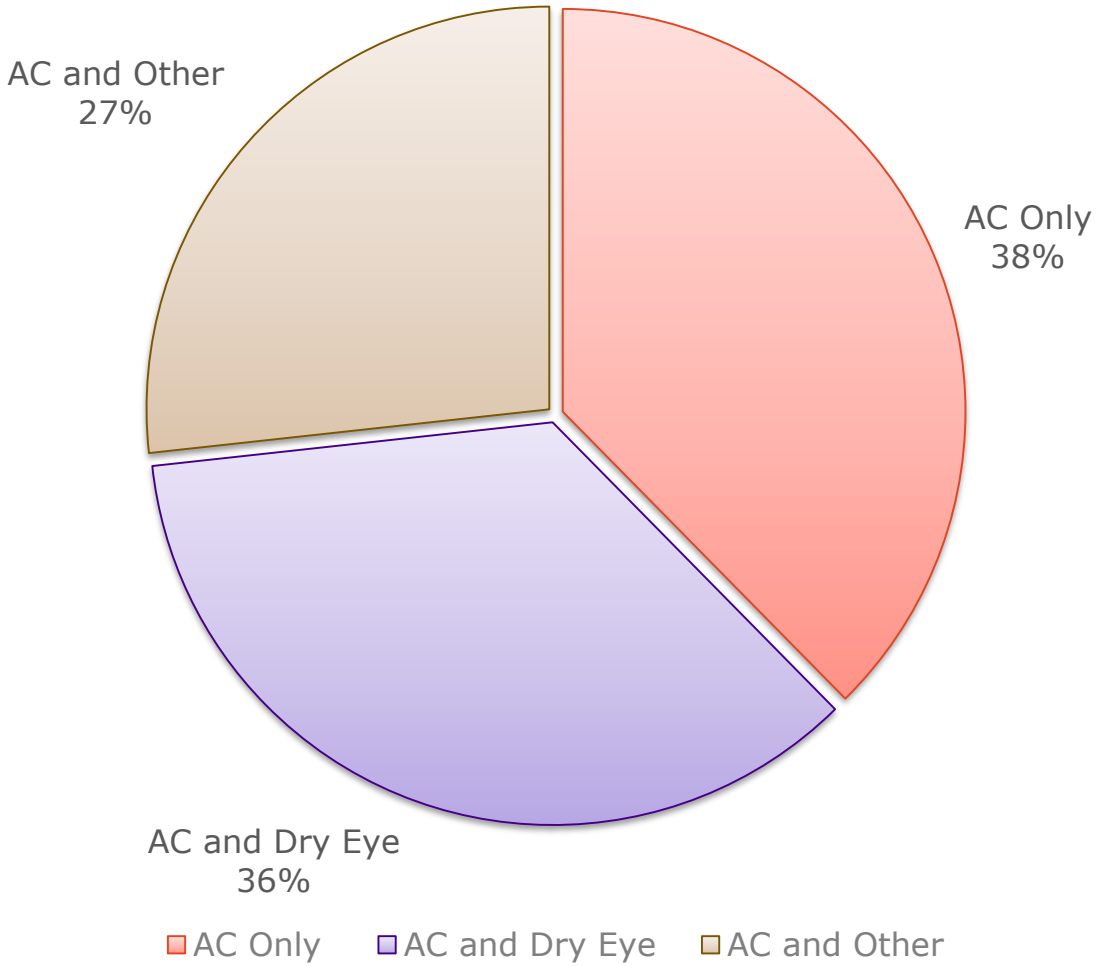
Source: Allergic conjunctivitis: a cross-sectional study; A. Leonardi et al; Clinical & Experimental Allergy, 2015 (45) 1118-1125.

What percentage of your AC patients on anti-histamines, after a single dose, fall into the following categories of symptom relief?



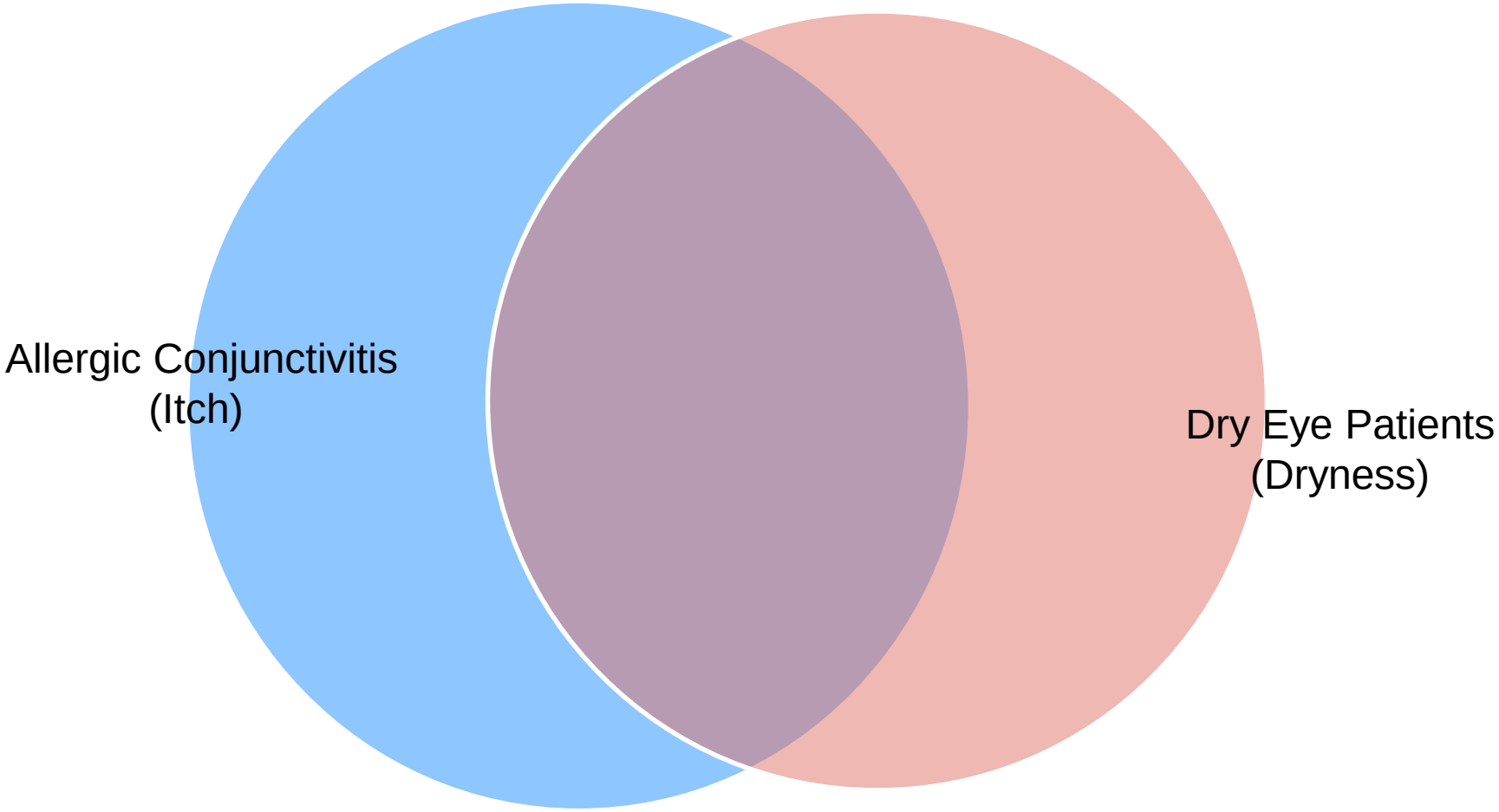
Source: GLG market research

What percentage of your AC patients have some type of mixed condition?



Source: GLG market research

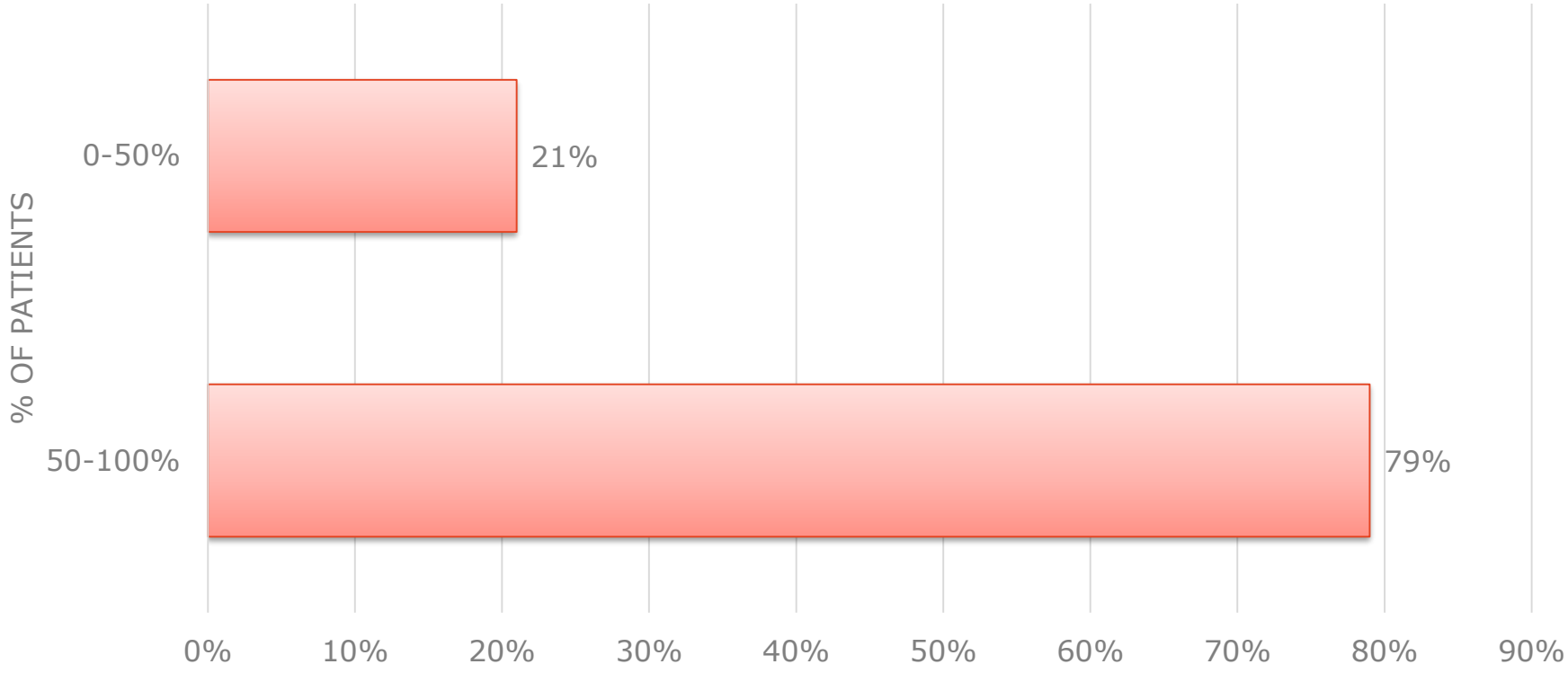
2011 Study of allergic conjunctivitis patients and dry eye syndrome consistent with survey results



45% of Allergic Conjunctivitis Patients with Itch Symptoms Also Experience Dryness

M.M. Hom et al. / Ann Allergy Asthma Immunol 108 (2012) 163–166

If a safe, non-steroidal, anti-inflammatory product was available that provided a more sustained symptomatic response than antihistamines, what percent of your AC patients would be candidates for this therapy?



Source: GLG market research

Conclusions – ADX-102 has potential for differentiated profile in allergic conjunctivitis treatment

- ADX-102 has a novel therapeutic profile
  - In Phase 2 clinical trials, the largest reduction in itching occurred after typical antihistamine peak activity
  - This observation consistent with effect on aldehyde-mediated allergic response
  - Potential for positioning as treatment for allergic conjunctivitis and dry eye
- Despite common perceptions, antihistamine treatment of allergic conjunctivitis has significant limitations
  - Antihistamines work acutely following allergen exposure
  - Activity of antihistamines diminishes rapidly
- Physician survey showed large percentage of patients do not receive adequate therapy using antihistamines alone
  - Limited duration, effectiveness
  - Large population moves on to the corticosteroids
- Physician survey identified strong physician preference for product with ADX-102 therapeutic profile
  - Potential to provide more sustained relief
  - Potential to avoid patient exposure to side effects of corticosteroids

ALDEYRA THERAPEUTICS™

Additional Data on Aldehyde Biomarker Correlation with Clinical Efficacy from Phase 2a Dry Eye Disease Clinical Trial

David Clark, MD
Chief Medical Officer
Aldeyra Therapeutics

Dry Eye Disease
Phase 2a Clinical Design

Groups	Topical Ocular ADX-102 Formulations: • 0.1% ADX-102 • 0.5% ADX-102 • 0.5% (Lipid) ADX-102
Randomization	1:1:1 28-Day Four-Times-Daily Dosing
Enrollment	51 Patients with Dry Eye Disease
Primary Objective	Dose Selection for Phase 2b Based on Tolerability and Exploratory Efficacy
Endpoints	Standard Dry Eye Disease Signs and Symptoms

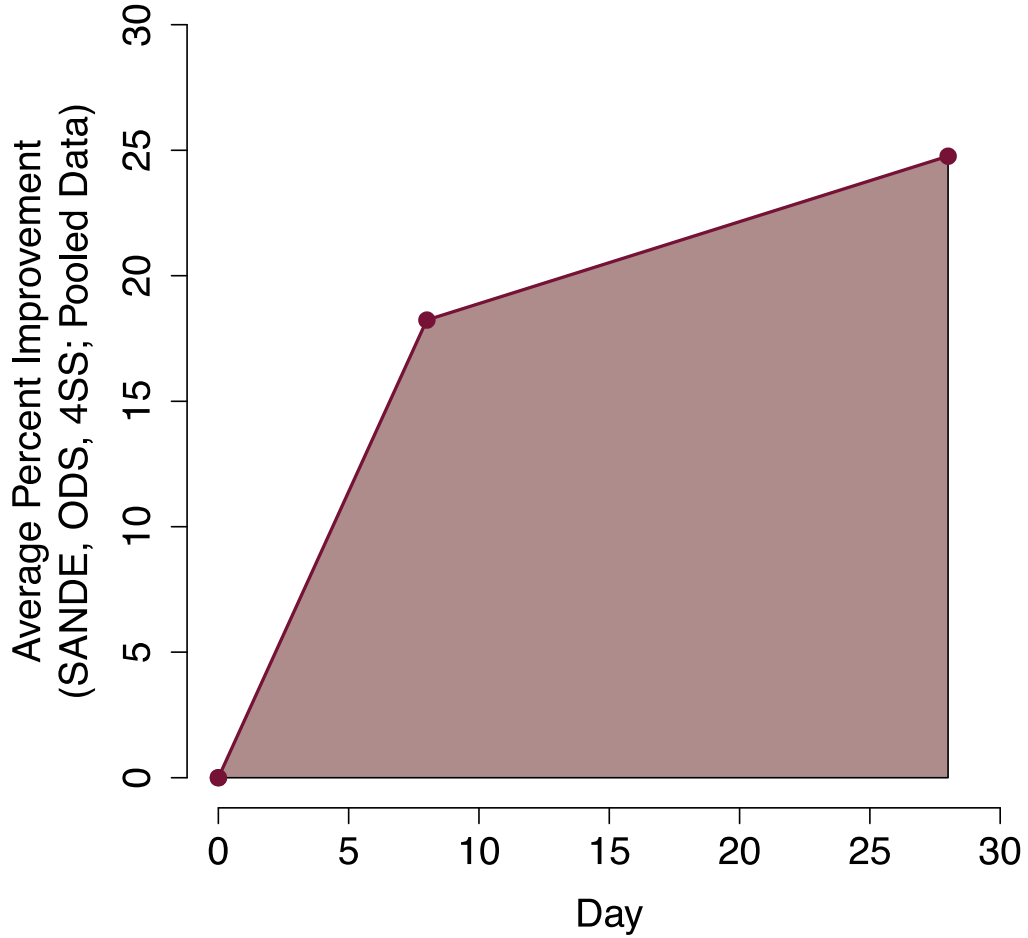
Further information can be found on www.clinicaltrials.gov: Trial #NCT03162783.

Statistically Significant Improvement in Multiple Dry Eye Disease Signs and Symptoms

Endpoint (Pooled Data)	Pre-Treatment	Post-Treatment	p value*
Symptom Assessment in Dry Eye (SANDE) Score	61	52	p = 0.003
Ocular Discomfort Score	2.3	1.5	p = 0.00002
Overall 4-Symptom Score	2.6	2.0	p = 0.0004
Tear Volume (Schirmer Test)	5.6	8.3	p = 0.008
Osmolarity	304	294	p = 0.003
Total Staining (Lissamine Green)	5.2	4.3	p = 0.002

p values are subject to change based on quality control analysis; Pre-Treatment = Day 0, Post-Treatment = Day 28.
Data from ADX-102 Phase 2a clinical trial.

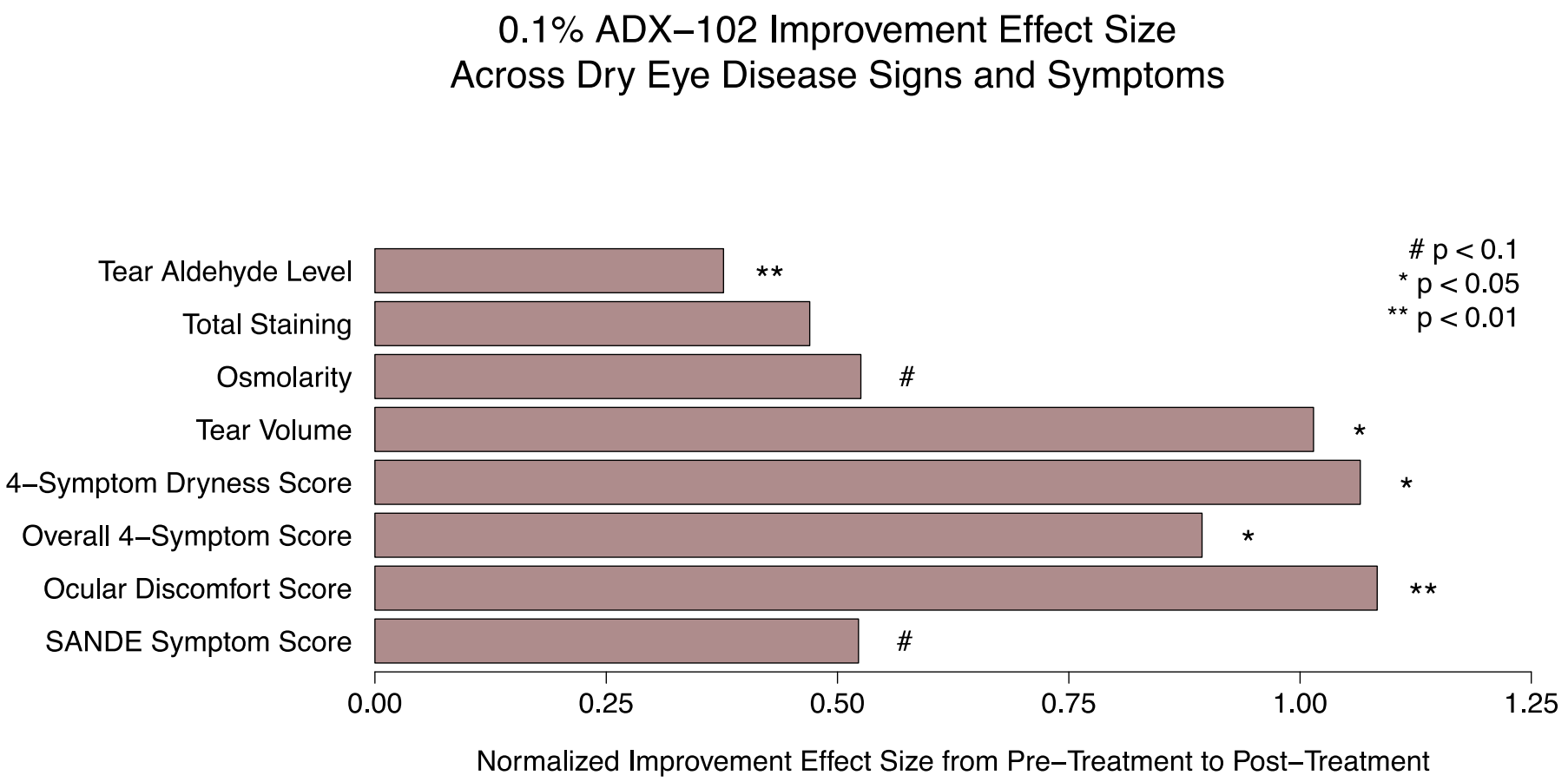
Symptom Improvement Over Time Supportive of Drug Activity



SANDE=Symptom Assessment in Dry Eye Score, ODS=Ocular Discomfort Score,
4SS=Overall 4–Symptom Score

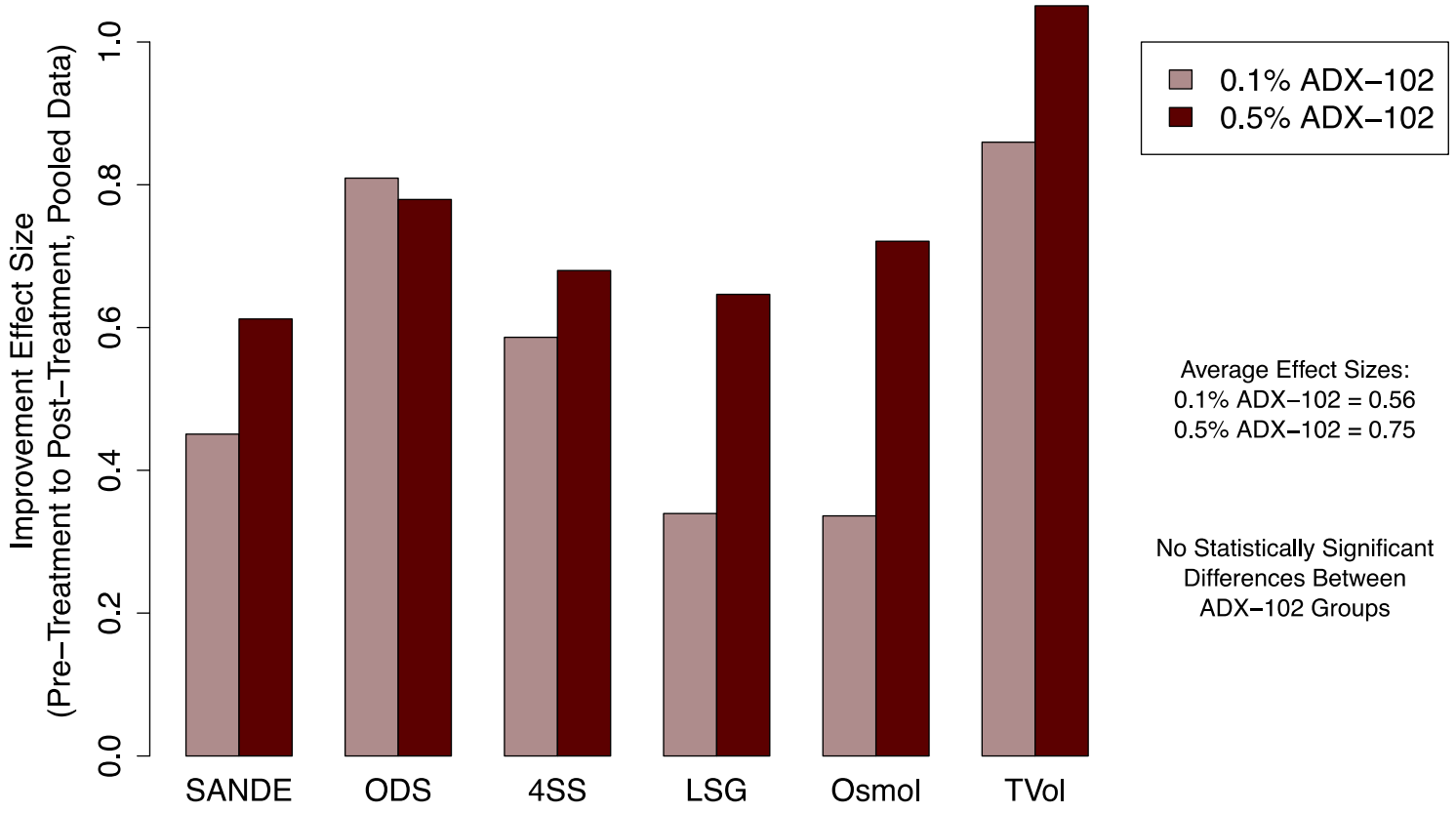
Pooled data from ADX-102 Phase 2a clinical trial.

Improvement Effect Sizes Were Robust and Statistically Significant



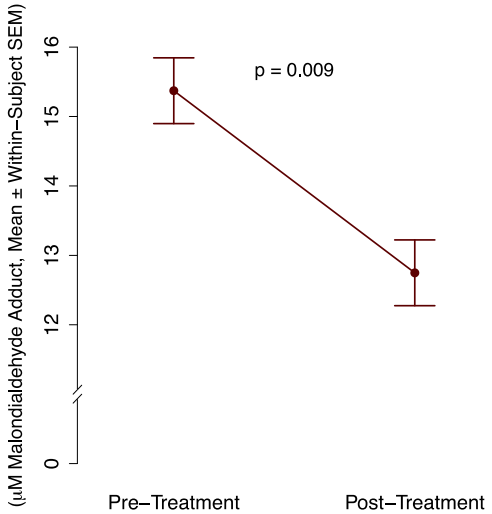
p values are subject to change based on quality control analysis; Effect size = Mean difference from Day 0 to Day 28 / Standard Deviation of Day 0. Data from ADX-102 Phase 2a clinical trial.

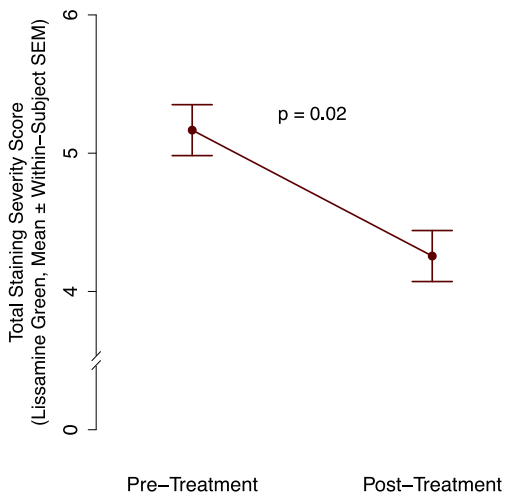
Dose Response in Phase 2a Dry Eye Disease Clinical Trial

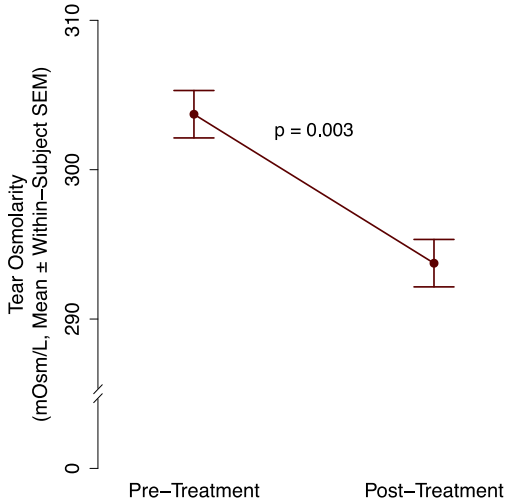


SANDE=SANDE Symptom Score, ODS=Ocular Discomfort Score,
4SS=Overall 4−Symptom Score, LSG=Lissamine Green Corneal Staining Score,
Osmol=Tear Osmolarity, TVol=Tear Volume (Schirmers Test)

Tear Aldehyde Reduction Supportive of ADX-102 Aldehyde Sequestering Mechanism



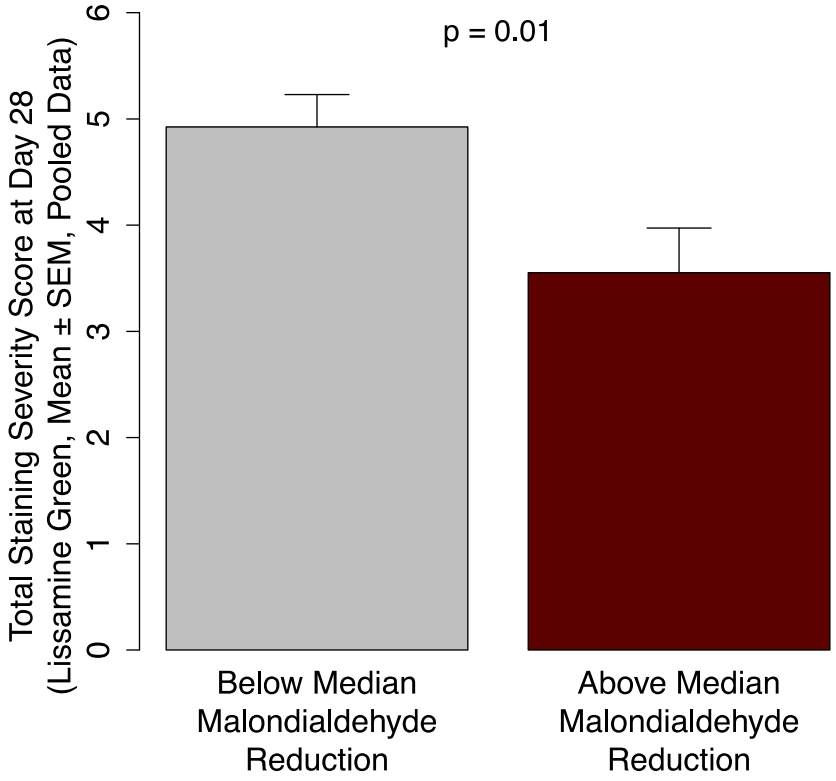




- Statistically significant aldehyde reduction occurred in conjunction with statistically significant reductions in ocular staining score and tear osmolarity.
- The results are consistent with published data correlating dry eye disease severity with increased aldehyde levels (Curr Eye Res 41: 1143, 2016).
- To our knowledge, our data are the first report of drug biomarker changes correlated with clinical efficacy.

p values are subject to change based on quality control analysis; Pre-Treatment = Day 0, Post-Treatment = Day 28; pooled data from Phase 2a clinical trial.

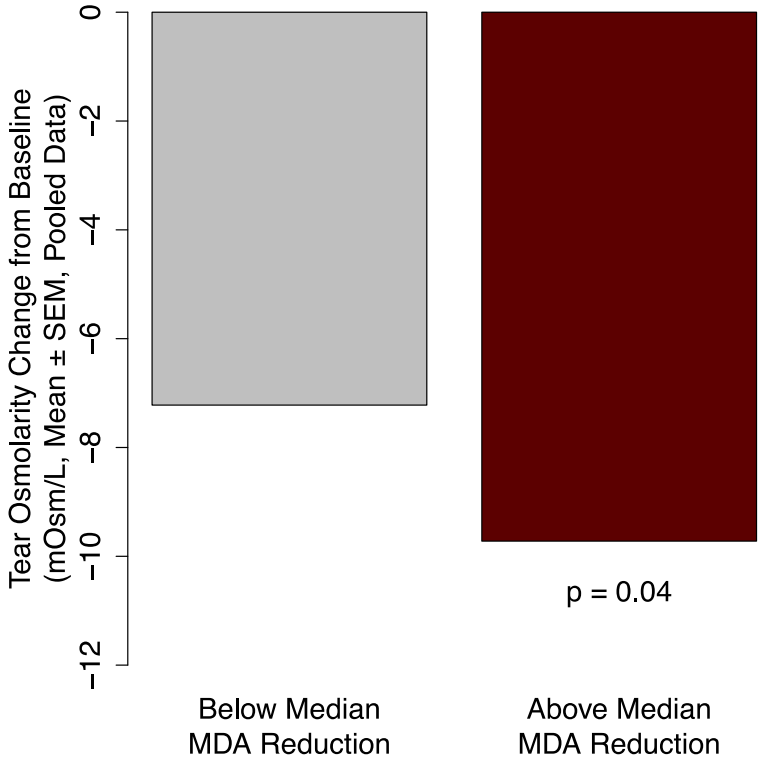
Aldehyde Reduction Correlated with Sign Improvement Within Individual Patients



Patients with the most reduction in aldehyde levels also exhibited greater corneal staining improvement, suggesting that aldehyde reduction is correlated with treatment efficacy in dry eye disease.

p values are subject to change based on quality control analysis; pooled data from Phase 2a clinical trial.

Aldehyde Reduction Correlated with Sign Improvement Within Individual Patients



Patients with the most reduction in aldehyde levels also exhibited greater tear osmolarity improvement, suggesting that aldehyde reduction is correlated with treatment efficacy in dry eye disease.

p value vs. baseline is subject to change based on quality control analysis; pooled data from Phase 2a clinical trial.

Dry Eye Disease
Expected Phase 2b Clinical Design*

Groups	0.1% ADX-102, 0.25% ADX-102, and Control
Randomization	1:1:1 Double-Masked
Treatment Time	12 Weeks
Enrollment	225 Patients with Dry Eye Disease
Endpoints	Standard Dry Eye Disease Signs and Symptoms

*Pending additional non-clinical data and other factors, which may not be in Aldeyra's control

Clinical and Regulatory Opportunities in Treatment of Dry Eye Disease

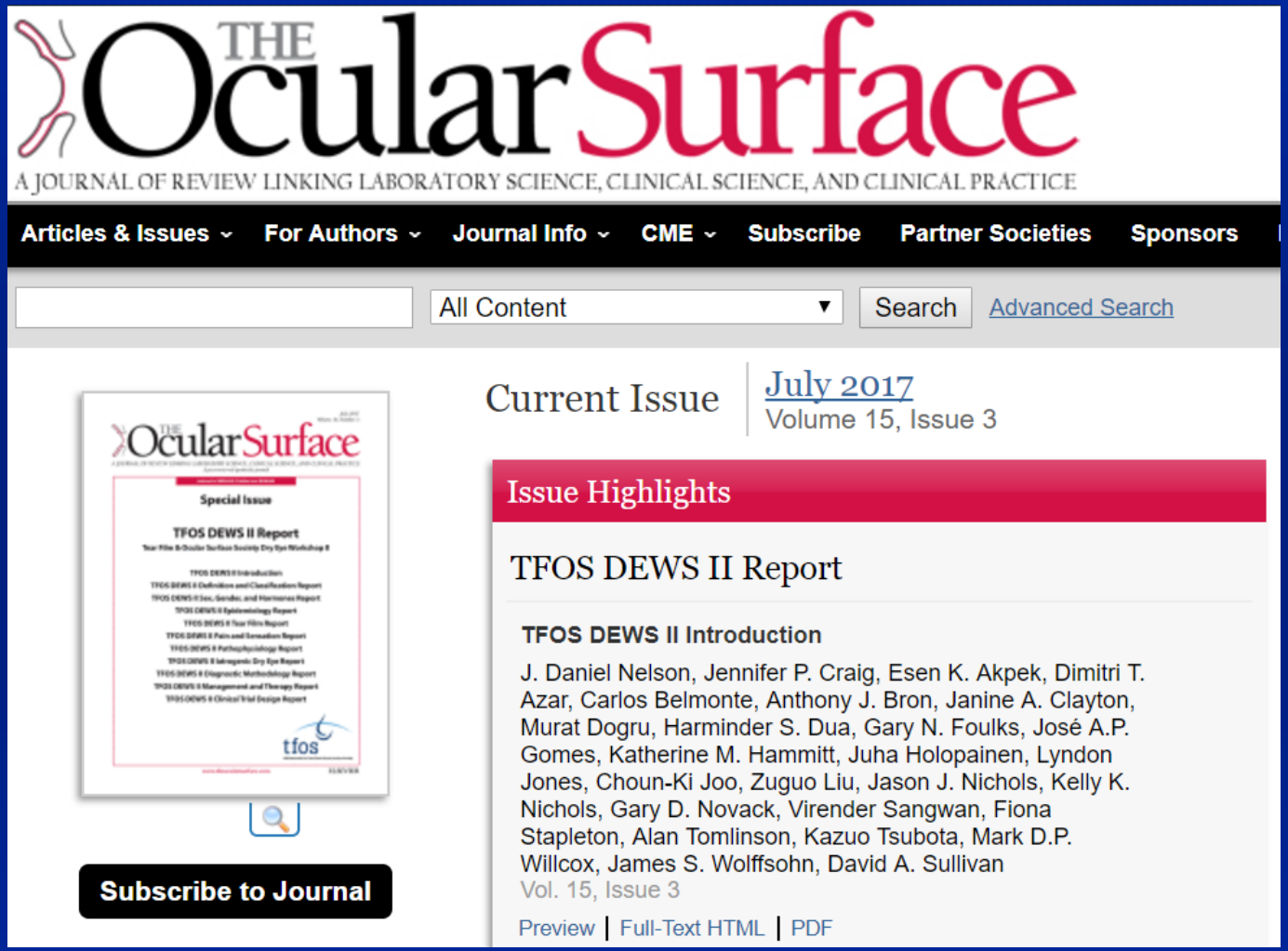
Gary D. Novack, Ph.D.

October 2017

The opinions expressed herein are those of Dr. Novack and do not necessarily reflect the views of Aldeyra.

Disclosures

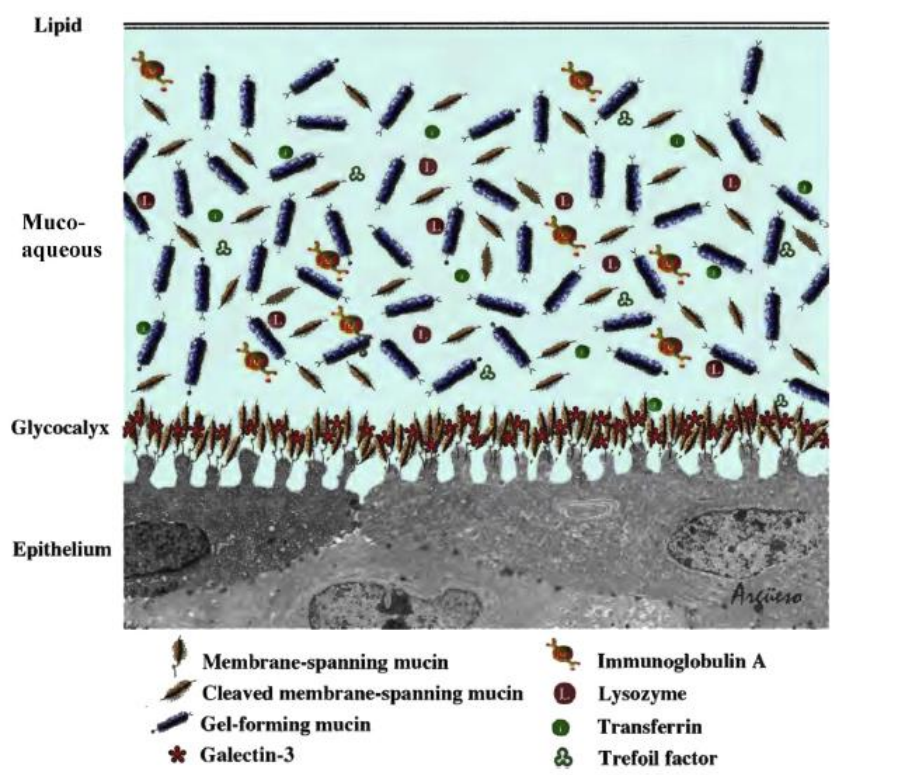
- Dr. Novack consults for numerous pharmaceutical and medical device firms.



Dry eye disease

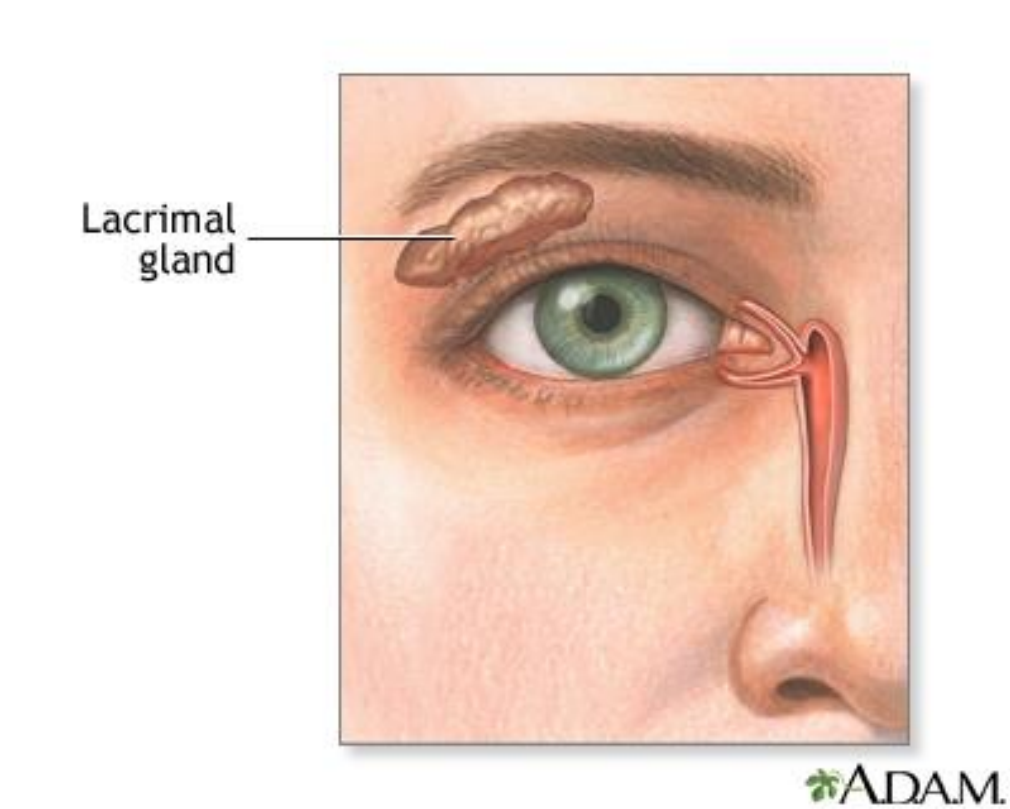
- Dry eye disease
- KCS
  - King Charles Spaniel
- Keratoconjunctivitis sicca
- Misnomer
  - Implies aqueous deficiency – which is only part of dry eye

Tear film

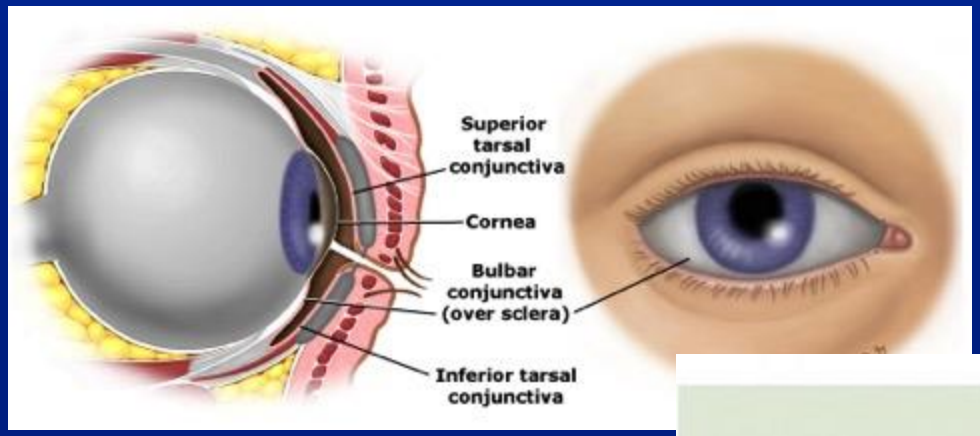


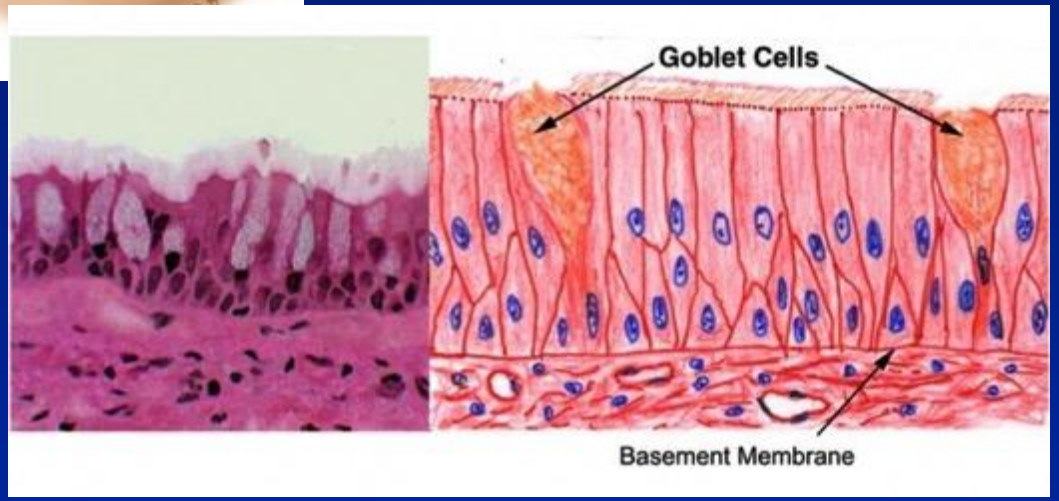
Willcox MDP et al TFOS DEWS II Tear Film Report. Ocul Surf 2017;15(3): 366-403.

Source of Tears: Aqueous

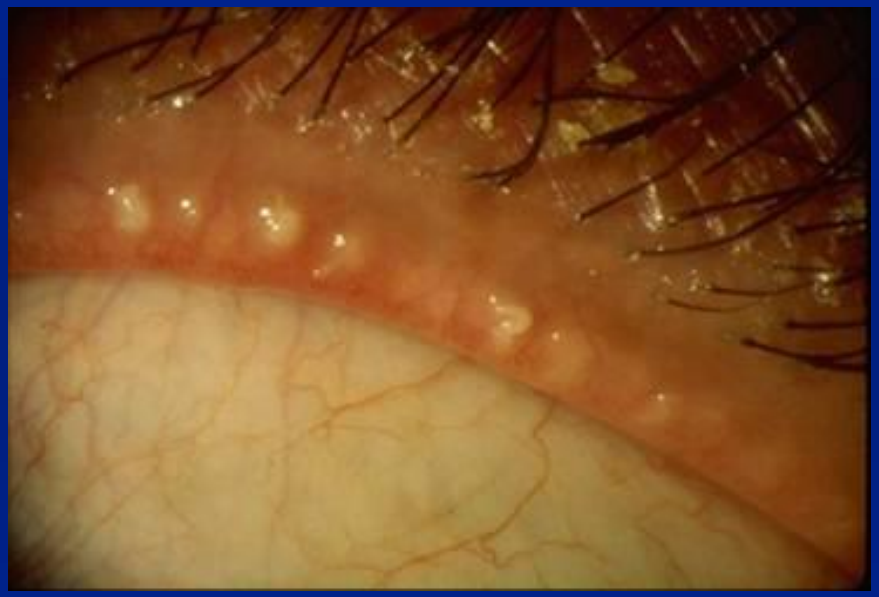


Source of Tears: Mucin



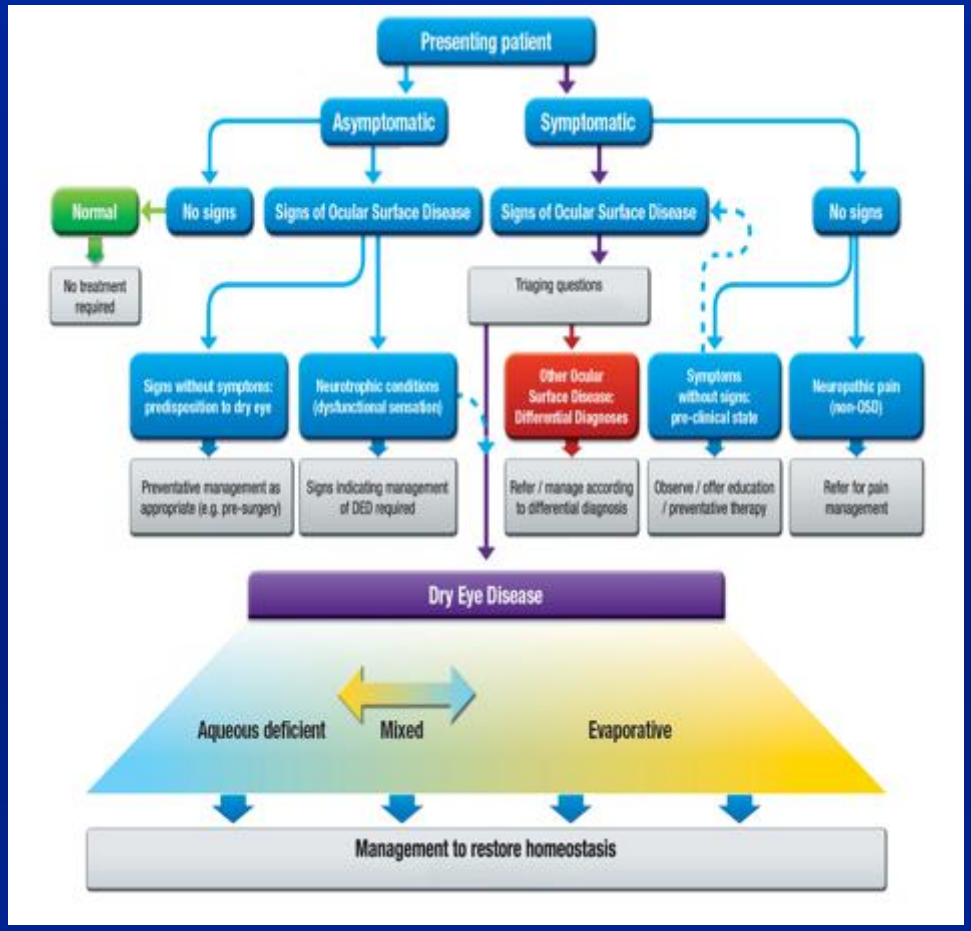


Source of Tears: Lipid



DEWS II definition of dry eye

- “Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles.”



Craig, JP et al. TFOS DEWS II Definition and Classification Report. Ocul Surf 2017;15(3): 276-283.

Treatments

The Ocular Surface xxx (2017) 580–634

Contents lists available at ScienceDirect

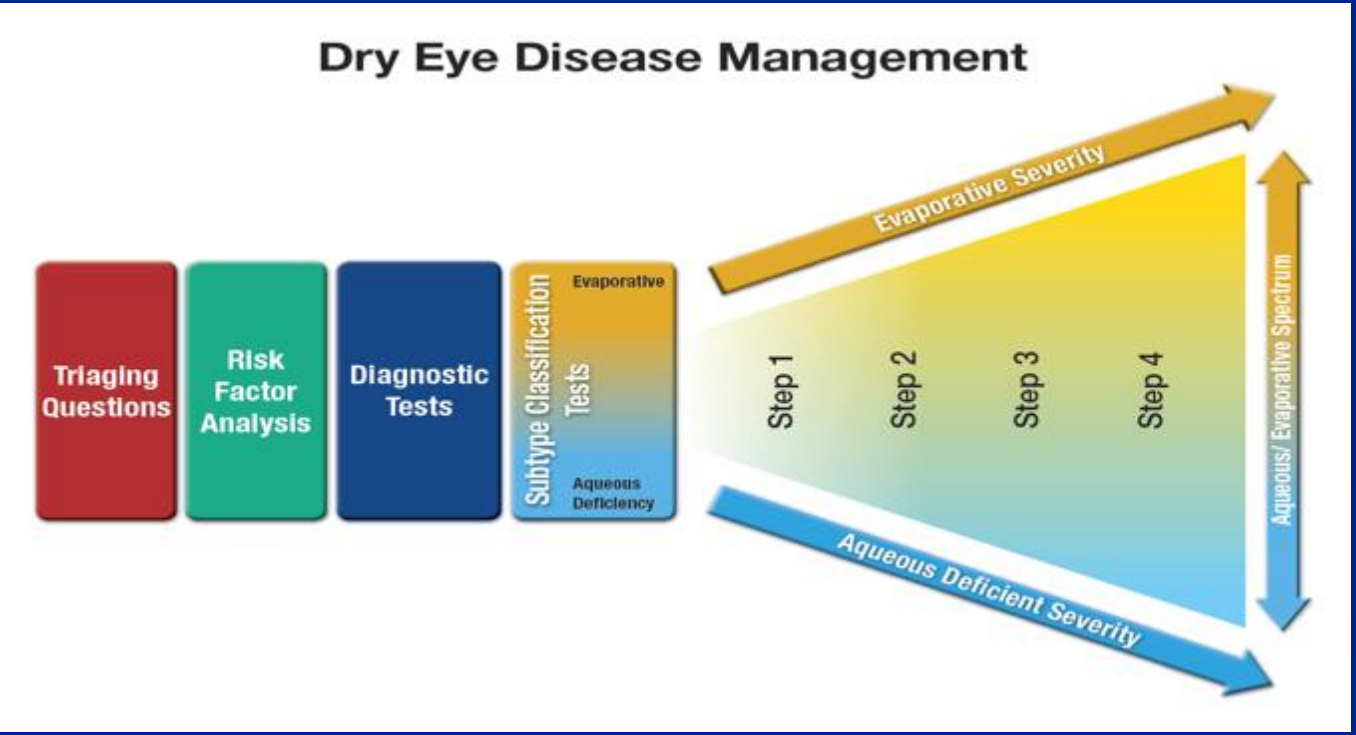
The Ocular Surface

journal homepage: www.theocularsurface.com

TFOS DEWS II Management and Therapy Report

Lyndon Jones, FCOptom PhD [a,*], Laura E. Downie, BOptom PhD [b], Donald Korb, OD [c], Jose M. Benitez-del-Castillo, MD PhD [d], Reza Dana, MD [e], Sophie X. Deng, MD PhD [f], Pham N. Dong, MD [g], Gerd Geerling, MD FEBO [h], Richard Yudi Hida, MD [i], Yang Liu, MD [j], Kyoung Yul Seo, MD PhD [k], Joseph Tauber, MD [l], Tais H. Wakamatsu, MD PhD [m], Jianjiang Xu, MD PhD [n], James S. Wolffsohn, FCOptom PhD [o], Jennifer P. Craig, MCOptom PhD [p]

Treatment recommendations



Diagrammatic representation of the process associated with the management of DED

Step 1

- Education regarding the condition, its management, treatment and prognosis
- Modification of local environment
- Education regarding potential dietary modifications (including oral essential fatty acid supplementation)
- Identification and potential modification/elimination of offending systemic and topical medications
- Ocular lubricants of various types (if MGD is present, then consider lipid containing supplements)
- Lid hygiene and warm compresses of various types

Step 2

- Prescription drugs to manage DED
  - Topical antibiotic or antibiotic/steroid combination applied to the lid margins for anterior blepharitis (if present)
  - Topical corticosteroid (limited-duration)
  - Topical secretagogues
  - Topical non-glucocorticoid immunomodulatory drugs (such as cyclosporine)
  - Topical LFA-1 antagonist drugs (such as lifitegrast)
  - Oral macrolide or tetracycline antibiotics

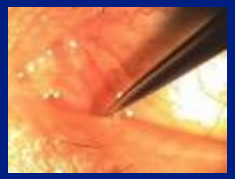
Investigational Rx

- Phase 3:
  - Loteprednol etabonate nanoparticles (Kala)
  - Tavilermide (Mimetogen / Allergan)
  - Cyclosporine OTX-101 (Auven/SunPharma)
  - Thymosin beta 4 – RegeneRx

Investigational Rx

- Phase 2:
  - P-321 (Parion/Shire)
  - Lubricin™ (Lubris/Novartis)
  - Lacritin™ (Tear Solutions)
  - ADX-102 (Aldeyra)

Treatments for Tear Insufficiency



- Tear replacement
  - Artificial tears (lubricants)
    - Aqueous supplements; Lipid supplements
  - Biological supplements
    - Autologous serum
- Tear conservation
  - Punctal occlusion
  - Moisture chamber spectacles
- Tear stimulation
  - Topical secretagogues; Oral secretagogues; Nasal neurostimulation

Ocular Lubricants

- Mainstay of therapy
  - numerous topical formulations available
- Avoid preservatives in severe dry eye
- Very few RCT have compared the relative superiority of a particular OTC product to others for DED

Anti-Inflammatory Therapy

- Topical glucocorticoids
- Non-glucocorticoid immunomodulators
  - Cyclosporine
  - Tacrolimus
  - NSAIDs
  - Biologics
- LFA-1 antagonist (Lifitegrast)
- Inflammatory modulation with systemic & topical antibiotics
  - tetracyclines
- Macrolide treatments

Surgical Approaches

- Tarsorrhaphy
- Surgical treatment for conjunctivochalasis
- Essential blepharospasm treatment with botulinum neurotoxin
- Lid corrections
  - Dermatochalasis
  - Blepharoptosis (ptosis)
  - Lower lid blepharoplasty
- Conjunctival surgery and amniotic membrane grafts
- Mechanical dacryoreservoirs
- Major salivary gland transplantation
  - Parotid duct transposition
  - Microvascular submandibular gland transplantation
- Minor salivary gland autotransplantation

Local Environmental Considerations

- Chronic topical medications
- Systemic medications
- Decreased blink rate
- Desiccating conditions and environmental pollutants
- Contact lens wear

US FDA: OTC Ophthalmic monograph

PART 349—OPHTHALMIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

Sec.

349.1 Scope.

349.3 Definitions.

Subpart B—Active Ingredients

Pharmacotherapy: Approvals

Table 17. Regulatory status of therapies for DED

Product	Country/Region (Year approved)			
	USA	Canada	Japan	Europe
Cyclosporine	Restasis® (2002)	Restasis® (2010)		Ikervis® (2015)
Hyaluronic Acid	—	—	Hyalein® (1995)	—
Diquafasol	—	—	Diquas® (2010)	—
Rebamapide	—	—	Mucosta® (2011)	—

Modified from Sullivan DA, Hammitt KM, Schaumberg DA, et al. Report of the TFOS/ARVO Symposium on global treatments for DED: an unmet need. Ocul Surf. 2012;10:108-16.

Chao W. Report of the Inaugural Meeting of the TFOS i(2) = initiating innovation Series: Targeting the Unmet Need for Dry Eye Treatment." Ocul Surf 2016;14(2): 264-316.

Xiidra®

NDA 208073

NDA APPROVAL

Shire Development LLC
Attention: Alida D. Barry
Manager, Global Regulatory Affairs
300 Shire Way
Lexington, MA 02421

/s/

JOHN J FARLEY
07/11/2016

Indications

- Restasis® (cyclosporine):
  - to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca.
- Xiidra® (lifitegrast):
  - For the treatment of the signs and symptoms of dry eye disease

FDA clinical efficacy requirements

- Two studies (per 1962 law)
- Efficacy:
  - One sign, one symptom
  - Statistically significantly different from vehicle
    - (or maybe) Non-inferior to approved product
- Safety: 300-500 subjects, 100 chronic

Intersection of Dry Eye Disease and Allergic Conjunctivitis

John D Sheppard, MD, MMSc
Professor of Ophthalmology, Microbiology & Molecular Biology
Clinical Director, Thomas Lee Ocular Pharmacology Laboratory
Ophthalmology Residency Research Director
Medical Director, Lions Eye Bank of Eastern Virginia
President, Virginia Eye Consultants
Norfolk, Virginia

The opinions expressed herein are those of Dr. Sheppard and do not necessarily reflect the views of Aldeyra.

Dry Eye Prevalence and Growth

- Dry eye prevalence estimates range from 14% to 33% of the general population
- 70% Female; 30% Males
- Common in Post-Menopausal Women
- Dry eye prevalence will continue its strong growth:
  - Aging population
  - Increasing visual tasking (computers, VDTs)
  - Worsening environmental factors (pollution, dry office environments)
  - Growing awareness by eye care providers, PCPs and patients through peers and DTC advertising

Level I Dry Eye: DEWS Report

Level II Dry Eye: DEWS Report

Dry Eye Rx Landscape: Restasis

- Restasis ® (0.05% cyclosporine ophthalmic emulsion)
- Approved by FDA on 12/23/2002
- Product Profile / Label:
  - Indication for treatment of a **sign only**: increased tear production
  - Onset of treatment effect: increased tear production observed after 6 months of treatment
  - Effective in 15% of patient population studied
  - Adverse effects:
    - **17%** of patients experienced ocular burning

Dry Eye Rx Landscape: Xiidra™

Xiidra ® (5% lifitegrast ophthalmic solution)

Approved by FDA on July 11, 2016

Product Profile / Label:

- Indication for treatment of the signs and symptoms of dry eye disease
- Adverse effects in **5-25%** of patients:
  - Instillation site irritation, dysgeusia and decreased visual acuity

xiidra™ (lifitegrast ophthalmic solution)5%

Dry Eye: A Fertile Landscape

- Large growing USA market with limited treatment options:
  - Restasis® approved product in US (2016 sales ~$1.4 billion)
  - Xiidra® approved product in the US (Aug-Dec 2016 ~ $54 million)
- Large growing International market with limited treatment options:
  - Ikervis® Ciclosporin 0.1% emulsion (Mar 2015, Europe, Santen)
  - Mucosta® Rebamipide 2% suspension (Sep 2011, Japan, Otsuka)
  - Hyalein® Sodium Hyaluronate 1% (April 2010, Japan, Senju)
  - Diquas® Diquofosol tetrasodium 3% solution (Dec 2010, Japan, Santen)

Dry Eye is an Inflammatory Condition

Well-supported in the Literature

Eastern Virginia Medical School

Dry Eye Disease

An Immune-Mediated Ocular Surface Disorder

William Stevenson, MD; Sunil K. Chauhan, PhD; Reza Dana, MD, MSc, MPH

Dry Eye Disease as an Inflammatory Disorder

Margarita Calonge, MD, Amalia Enríquez-de-Salamanca, PhD, Yolanda Diebold, PhD, María J. González-García, PhD, Roberto Reinoso, PhD, José M. Herreras, MD, and Alfredo Corell, PhD

ICAM-1 expression predisposes ocular tissues to immune-based inflammation in dry eye patients and Sjögrens syndrome-like MRL/lpr mice

Jianping Gao, Grant Morgan, David Tieu, Tammy A. Schwalb, Jessica Y. Luo, Larry A. Wheeler, Michael E. Stern*

Tear Cytokine Profiles in Dysfunctional Tear Syndrome

HELENE LAM, LAUREN BLEIDEN, CINTIA S. DE PAIVA, WILLIAM FARLEY, MICHAEL E. STERN, AND STEPHEN C. PFLUGFELDER

The Definition and Classification of Dry Eye Disease:
Report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop (2007)

Analysis of Inflammatory Cytokines in the Tears of Dry Eye Patients

Morgan L. Massingale, MS, Xiaohong Li, MD, PhD, Maithreyi Vallabhajosyula, OD, Dongmei Chen, MD, PhD, Yi Wei, DVM, PhD, and Penny A. Asbell, MD, MBA

Epithelial–Immune Cell Interaction in Dry Eye

Stephen C. Pflugfelder, MD, Cintia S. de Paiva, MD,* De-Quan Li, MD, PhD,* and Michael E. Stern, PhD*†*

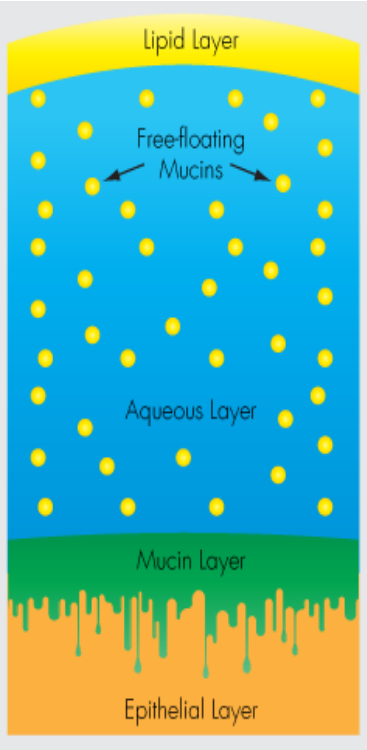
Conjunctival Epithelium Expression of HLA-DR in Dry Eye Patients

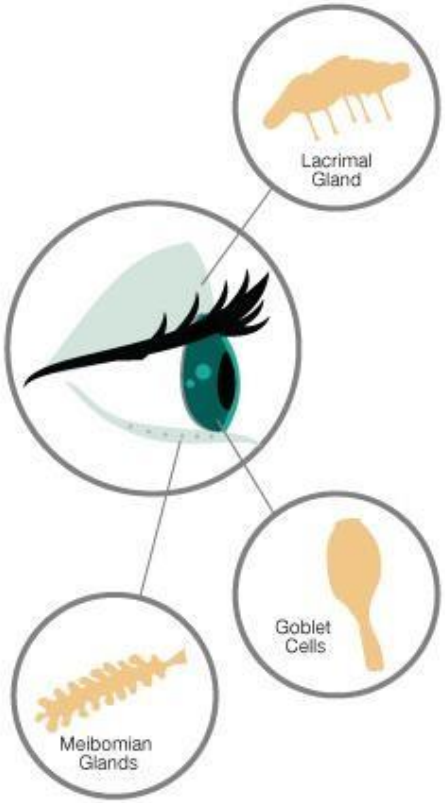
Kazuo Tsubota[a,b,c] Tsutomu Fujihara[a] Keiko Saito[b] Tsutomu Takeuchi[d]

Conjunctival T-Cell Subpopulations in Sjögren's and Non-Sjögren's Patients with Dry Eye

Michael E. Stern,[1] Jianping Gao,[1] Tammy A. Schwalb,[1] Mylinh Ngo,[1] David D. Tieu,[1] Chi-Chao Chan,[2] Brenda L. Reis,[1] Scott M. Whitcup,[3] Darby Thompson,[4] and Janine A. Smith[2]

Causes of Dry Eye

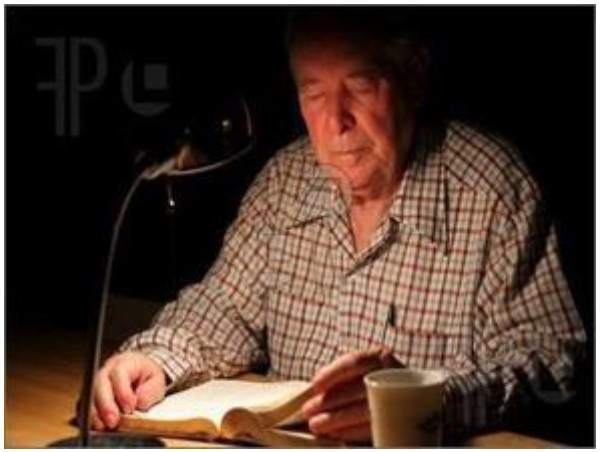




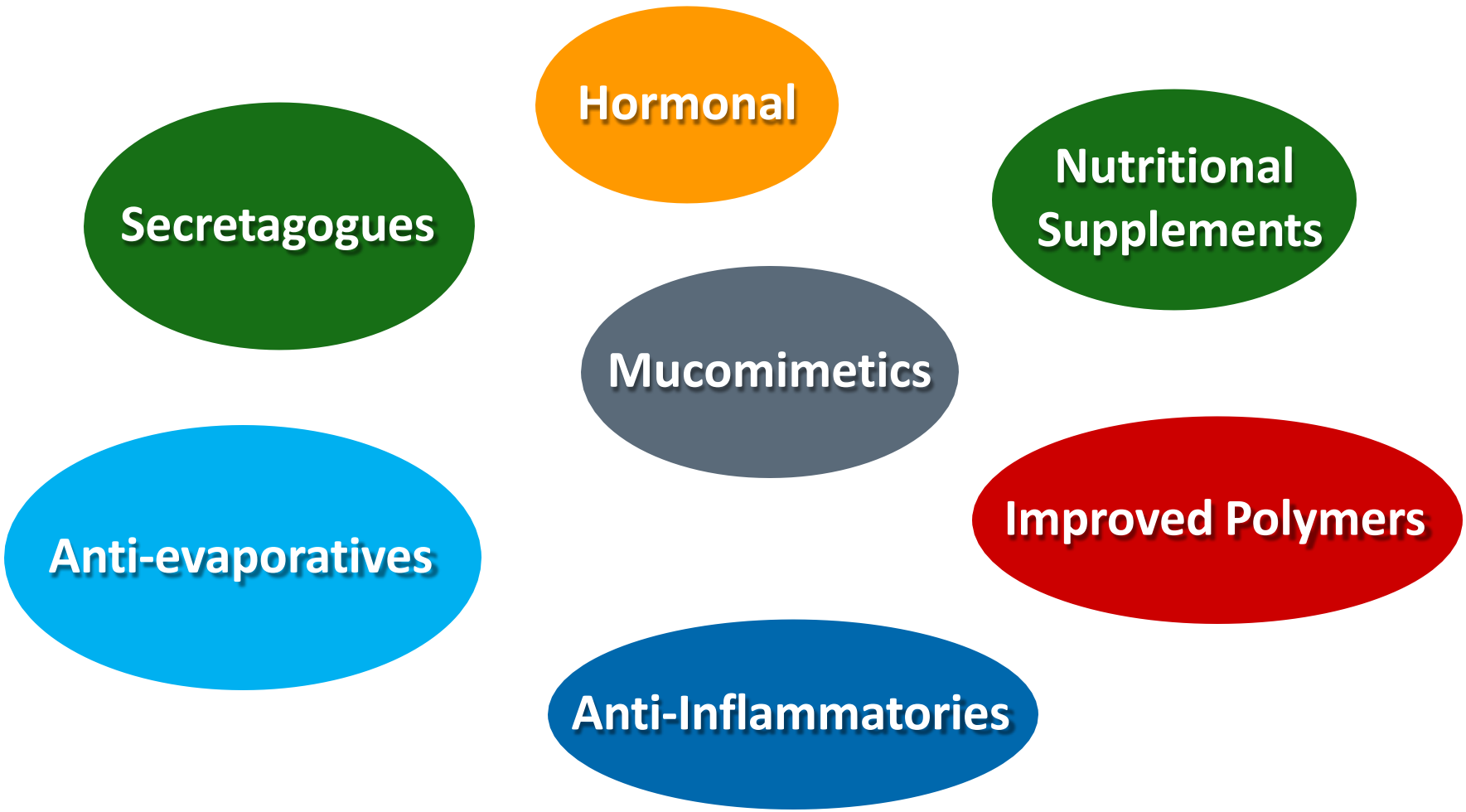
- Aqueous-Deficient
  - Autoimmune disease (Sjögren's Syndrome, RA, Lupus)
- Lipid-Deficient
  - Meibomian gland dysfunction, Hormonal changes
- Mucin-Deficient
  - Goblet cell loss
- Neural Loop-Associated
  - Abnormal corneal sensitivity, Blink disorders
- Environmentally Induced or Exacerbated

Environmental Factors

Corollary Factors

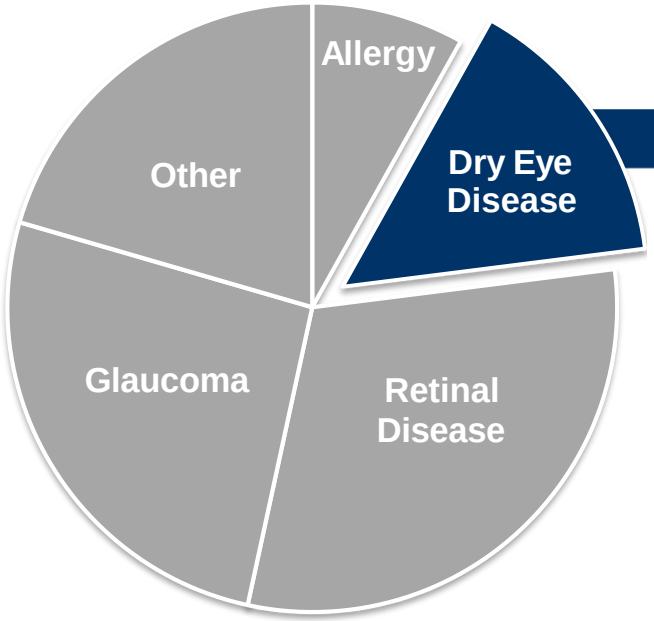


Therapeutic Approaches Under Investigation

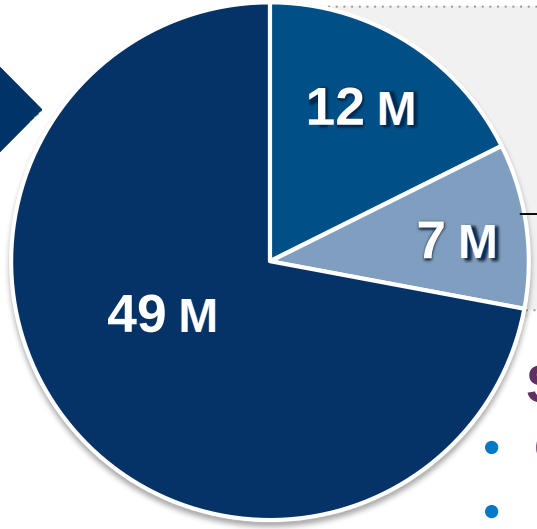


Significant Need for New Therapies for Dry Eye Disease

Total Global Ophthalmic Market- Large and Growing



Dry Eye Global Patient Population: 68 Million*



U.S. Market: 19 Million

Moderate to Severe

Standard of Care:

- OTC artificial tears
- Restasis®
- Off-label steroids

Dry eye disease is one of the leading causes of patient visits to eye care professionals in the U.S.

Commercial Opportunity:

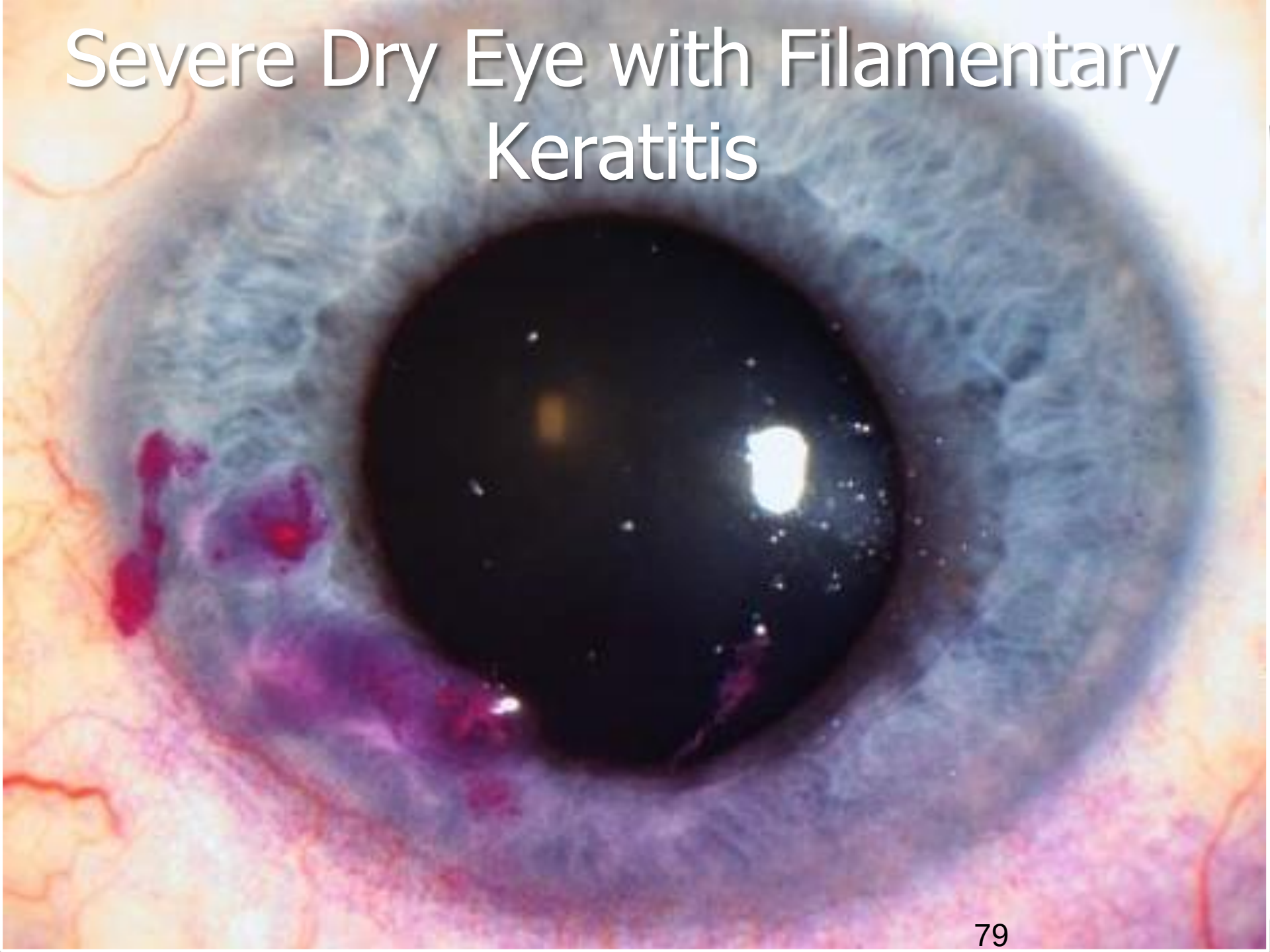
Reachable with a specialty sales force detailing to ophthalmologists & optometrists

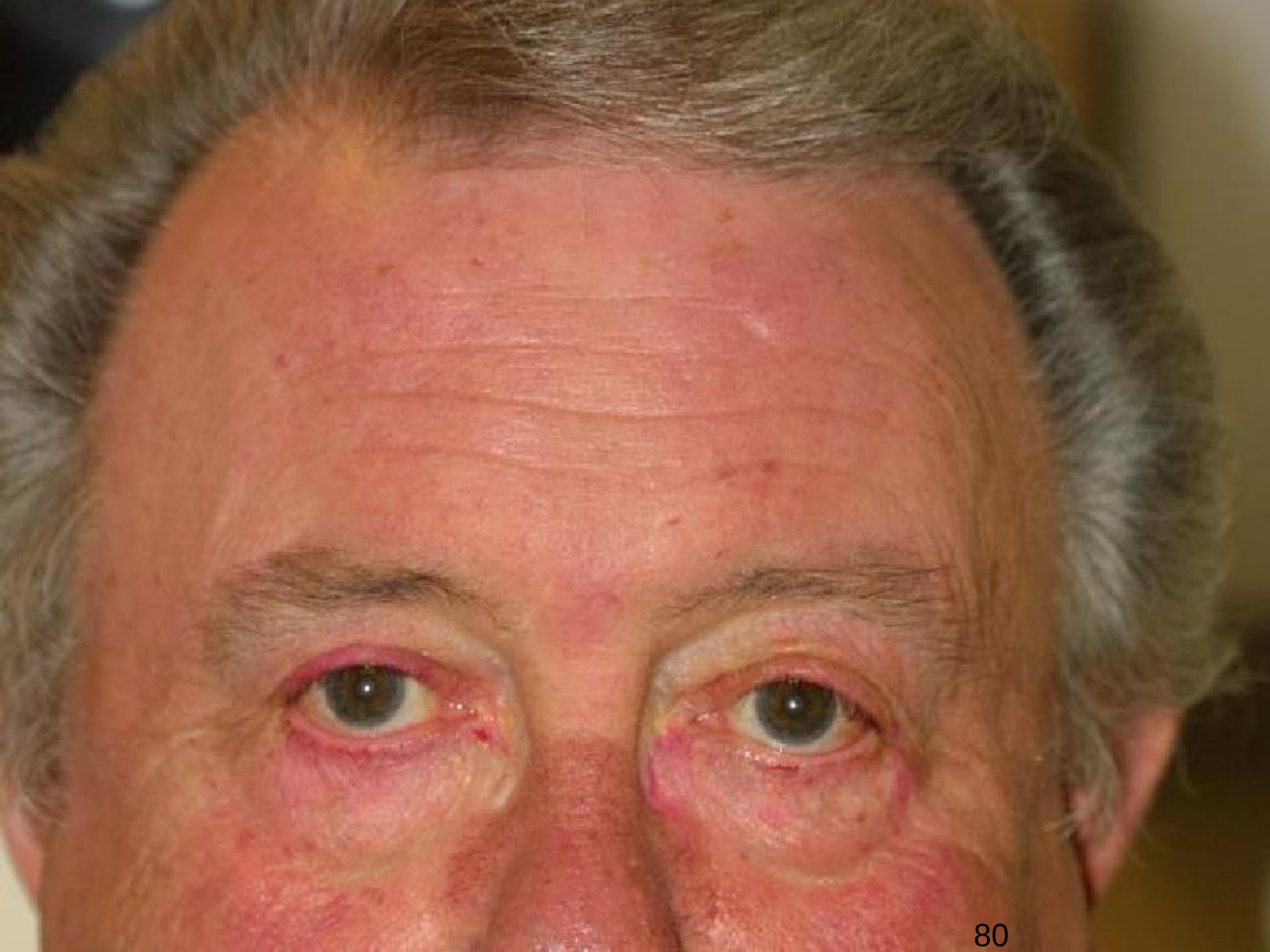
*Developed markets; Market Scope 2013

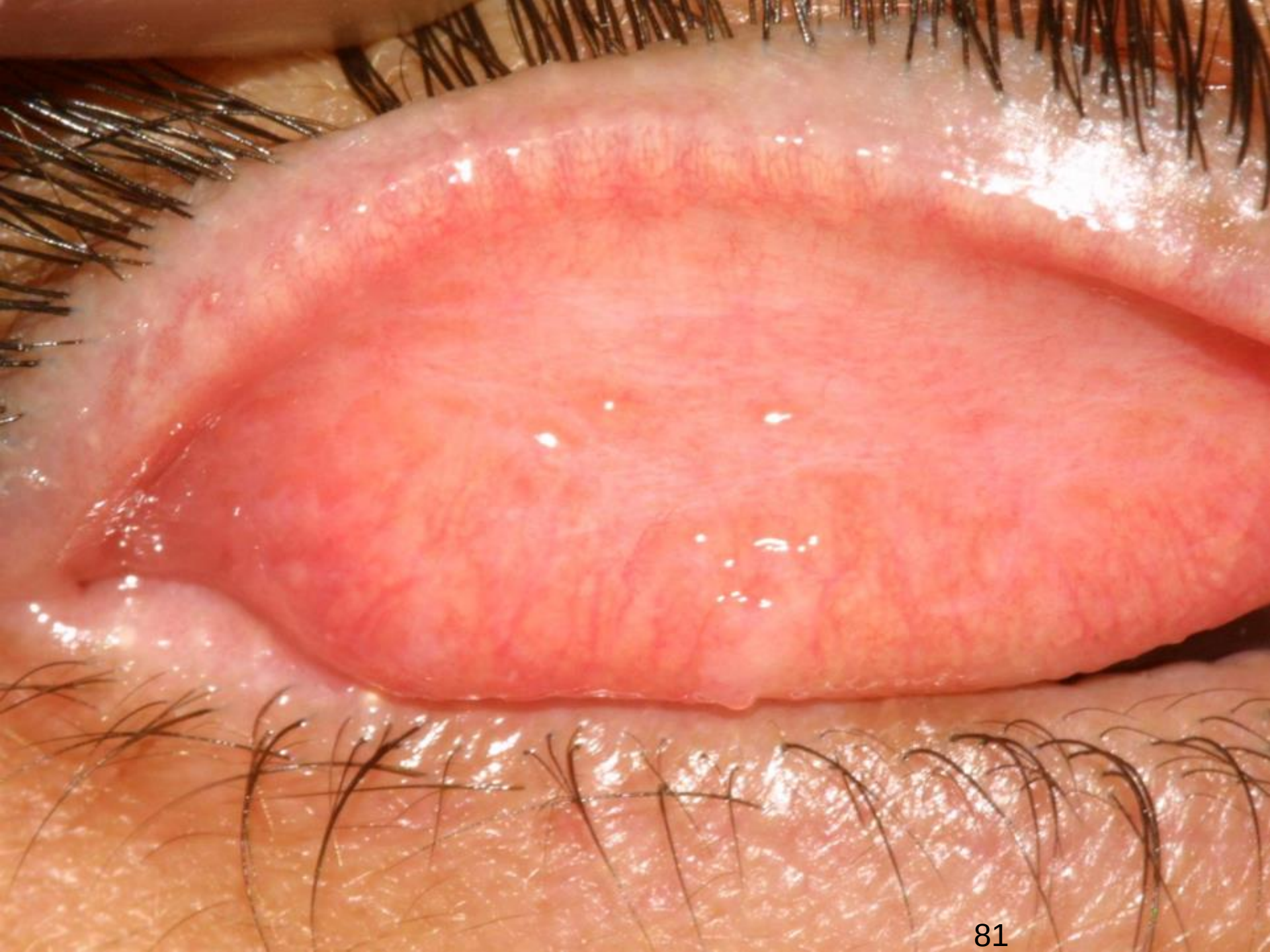
Dry Eye Complications

- Chronic Discomfort
- Foreign Body Sensation
- Visual Fluctuations
- Decreased Productivity
- Depression
- Contact Lens Intolerance
- Poor Surgical Predictability & Outcomes
- Infectious Keratitis

Severe Dry Eye with Filamentary Keratitis

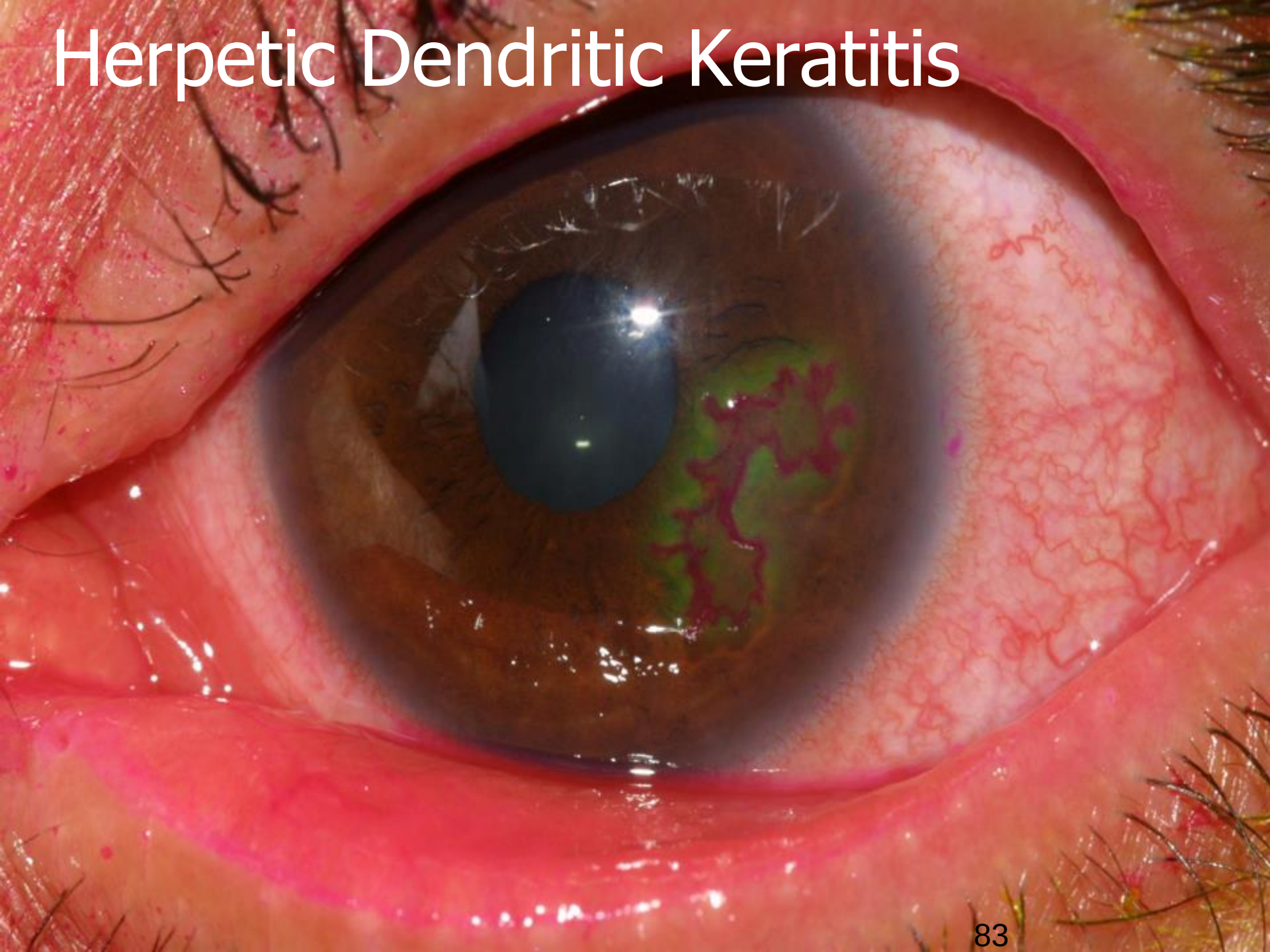


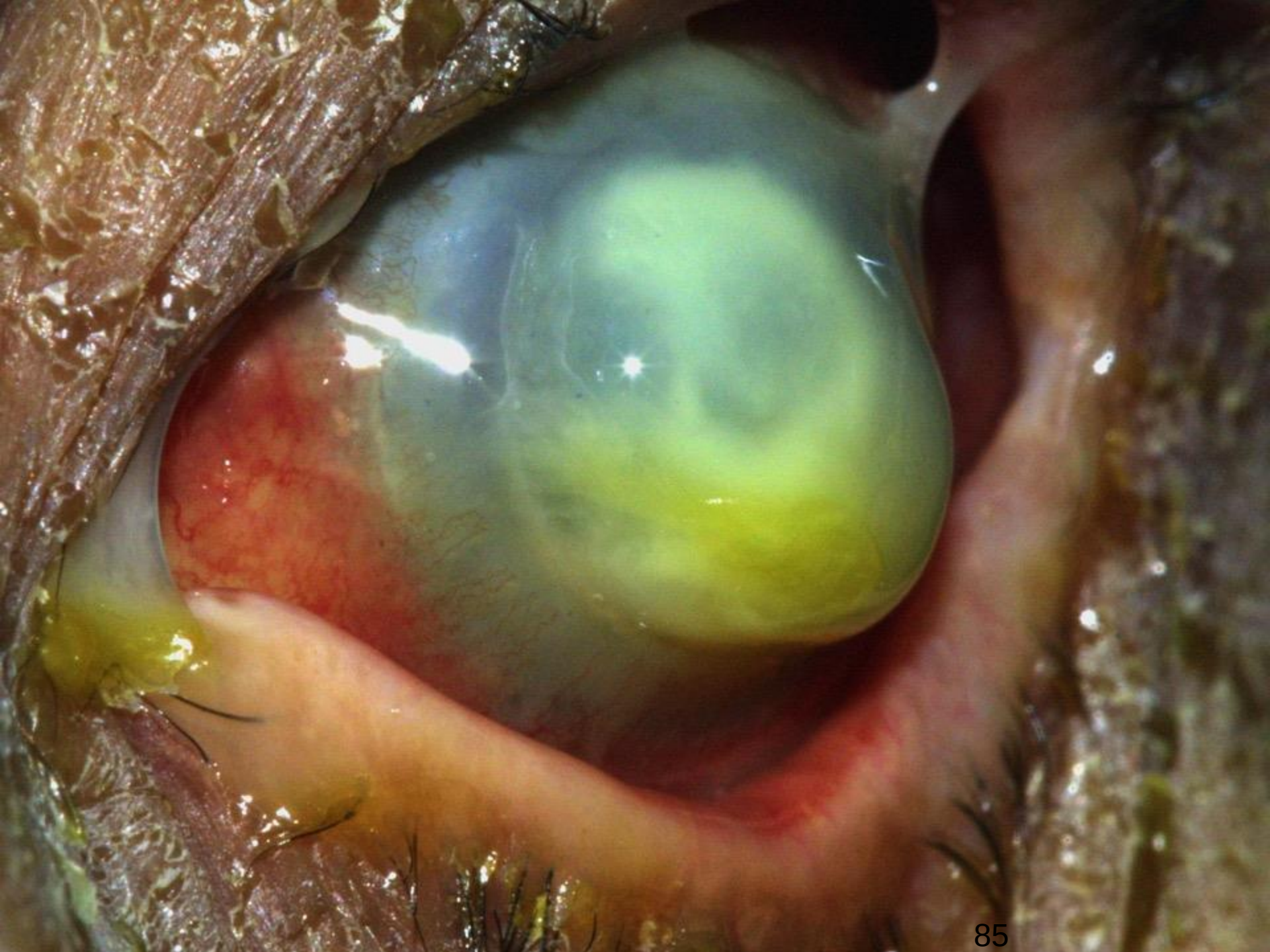


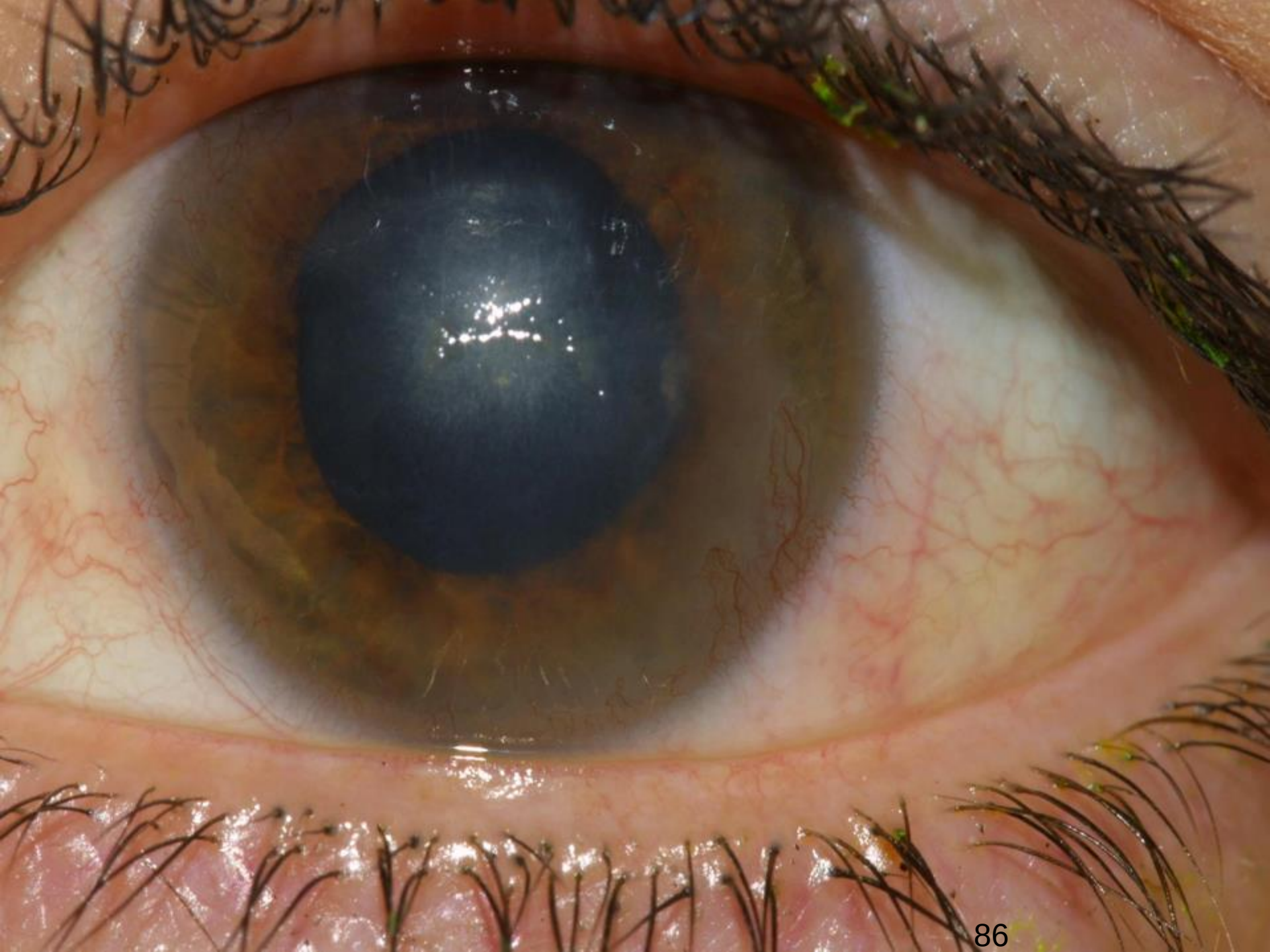


Dry Eye & Rheumatoid Arthritis
Peripheral Ulcerative Keratitis

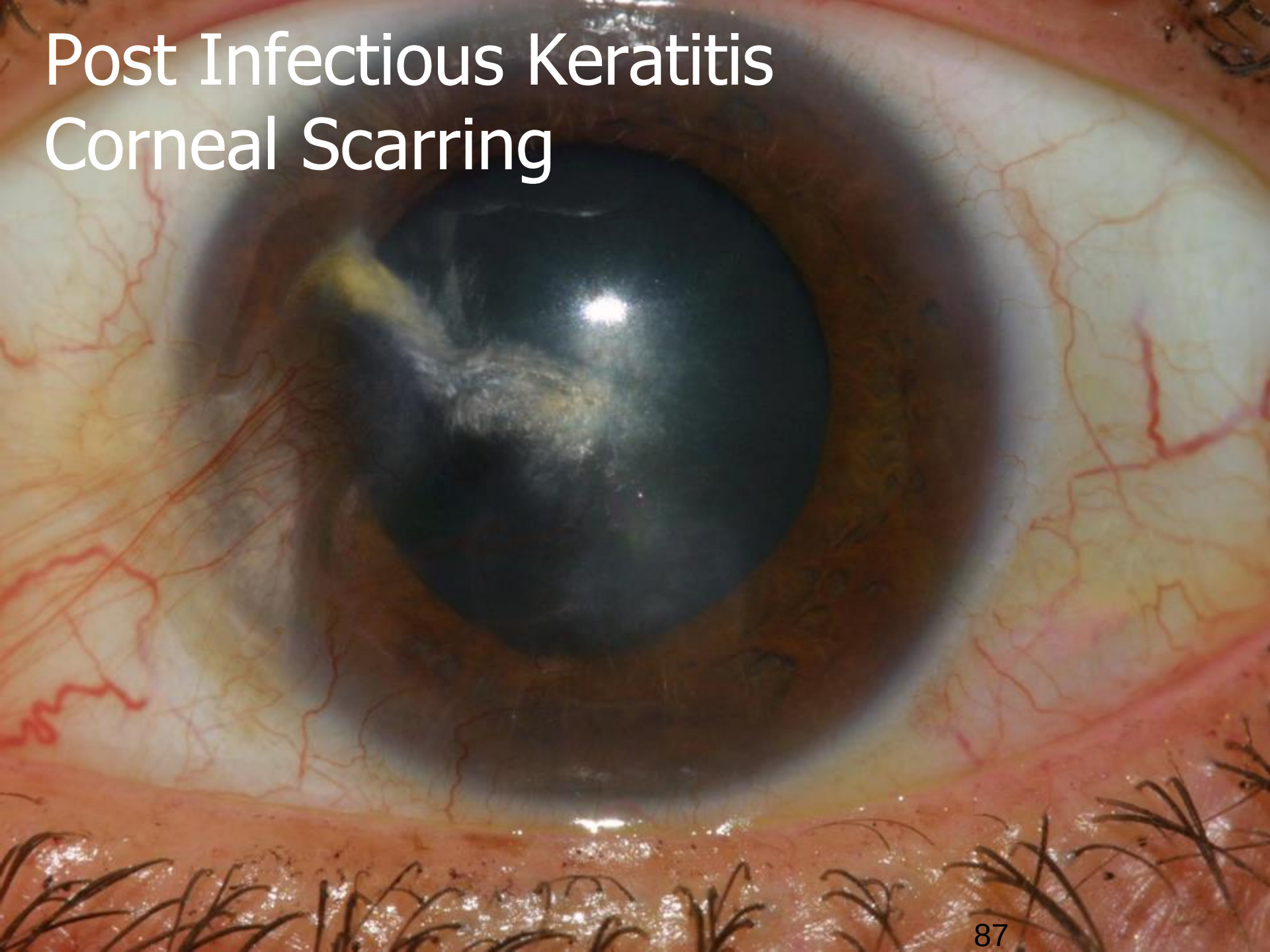
Herpetic Dendritic Keratitis

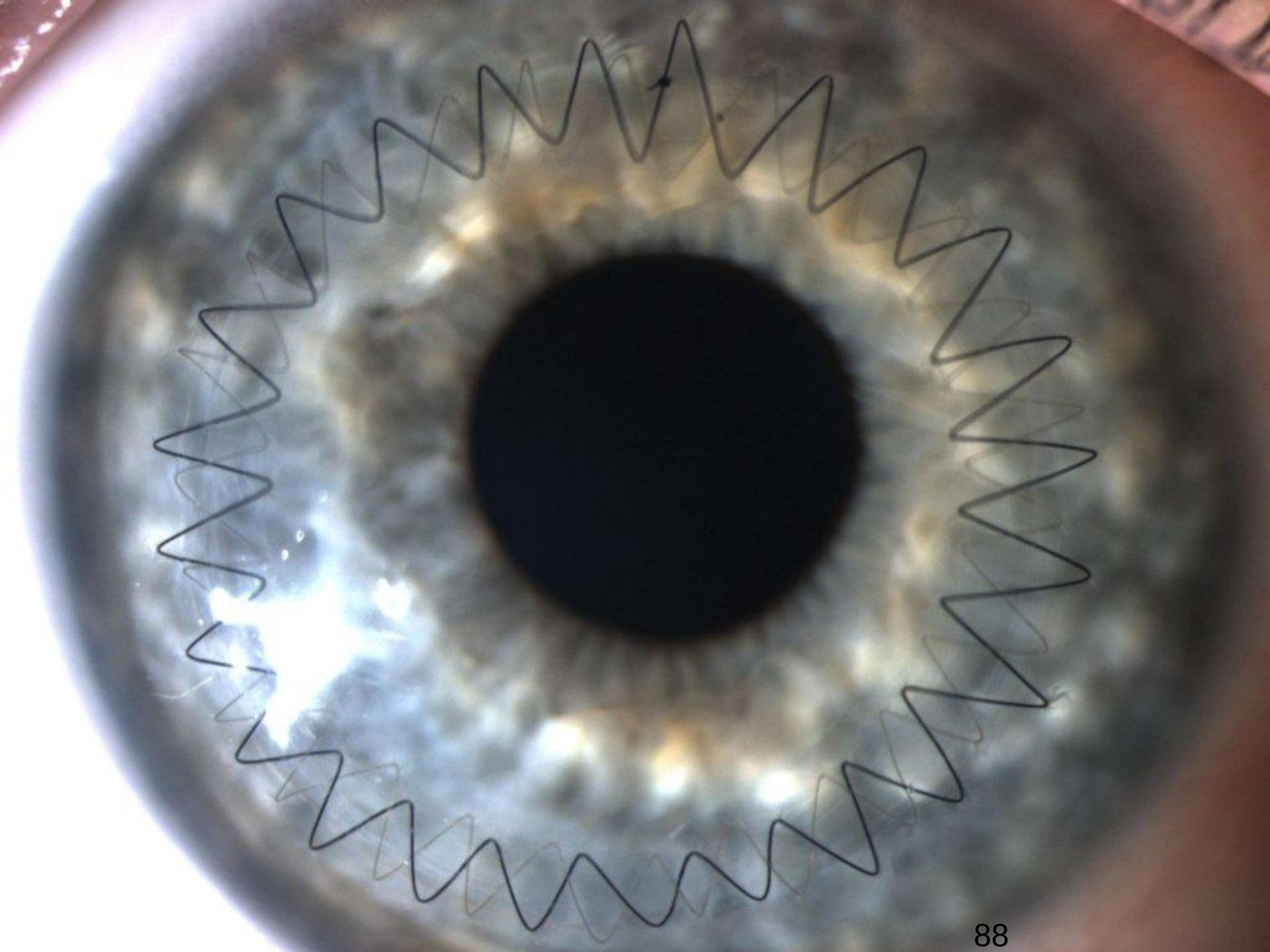






Post Infectious Keratitis Corneal Scarring





Tecnis Symfony IOL (AMO)


ReStor
Multifocal
Intraocular
Lens
(Alcon)

Crystalens Accomodating Intraocular Lens (Bausch & Lomb)

DRY EYES?

VIRGINIA eye consultants

CATARACTS?

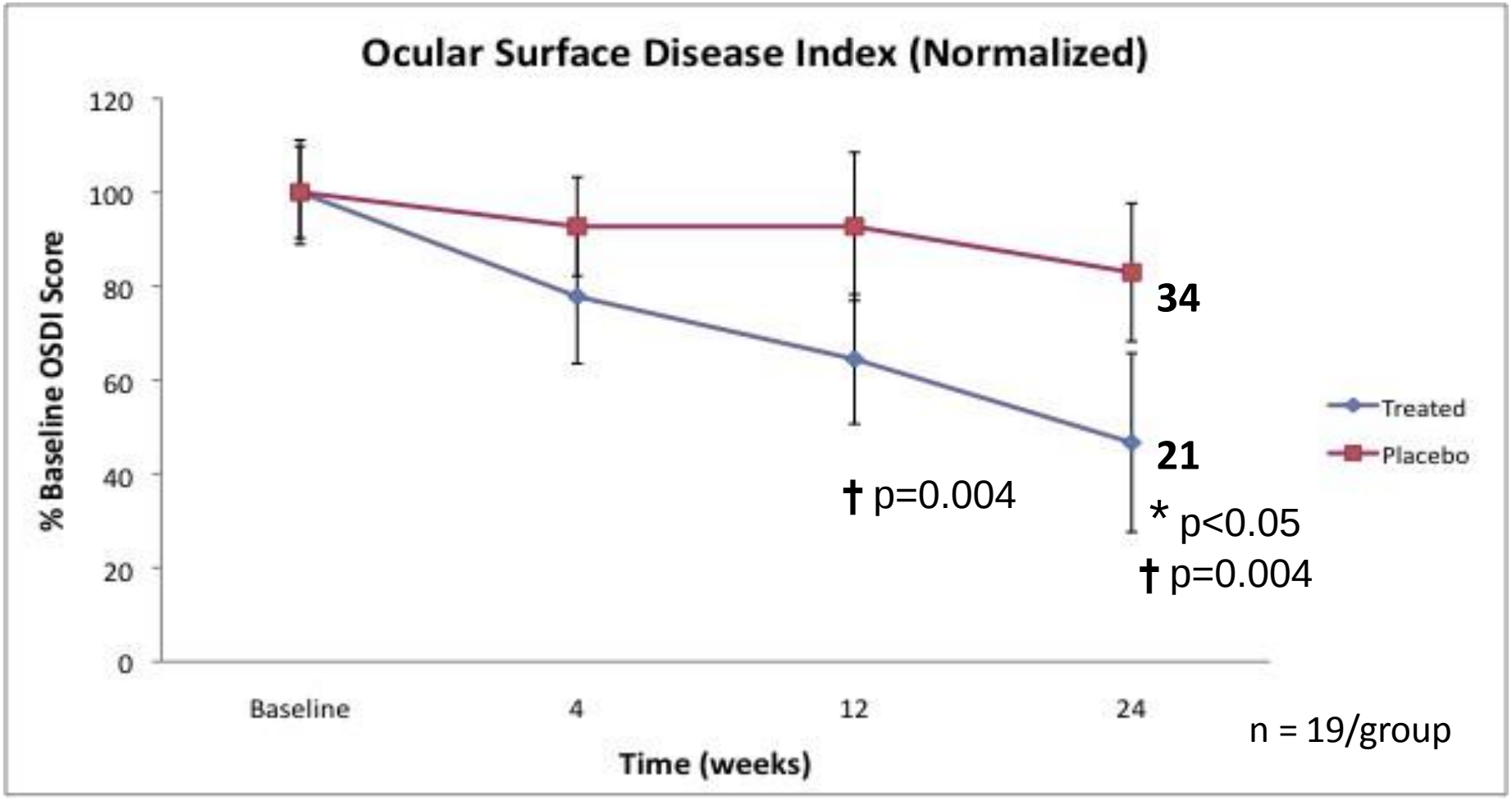
VIRGINIA eye consultants

Multiple Risk Factors

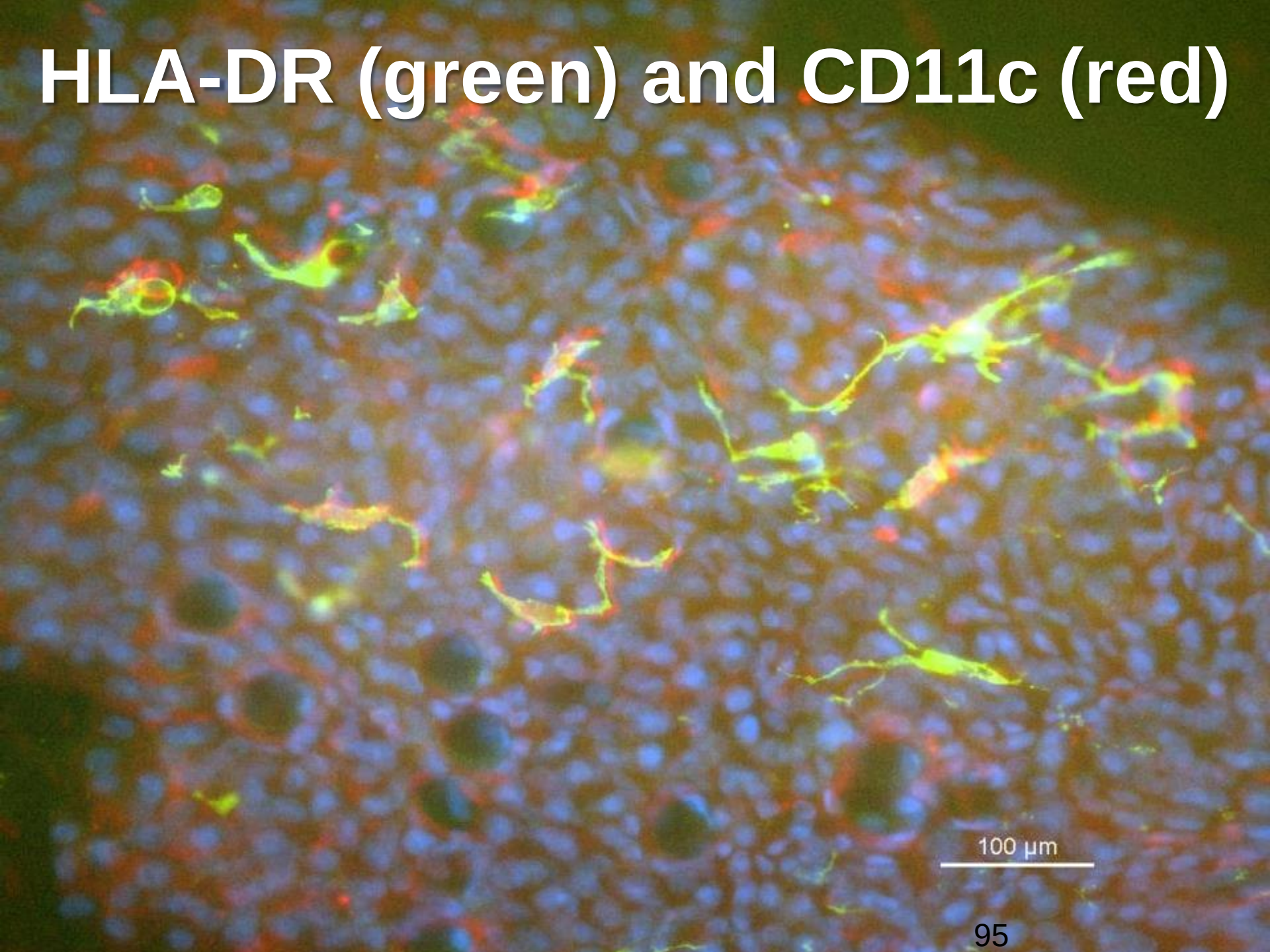
- Older Age
- Androgen Deficit: Female Sex, Prostate Cancer Rx
- Auto-Immune Disease: Sjogrens, RA, SLE
- Ocular Co-morbidity: Lids, MGD, Allergy, Surgery
- Cutaneous Disease: Rosacea, Eczema
- Poor Diet: Low Omega-3, High Fat
- Medications: Topical, Systemic
- Neurologic: Senescent Blink, Neurotrophic

1.Pflugfelder et al. *Cornea.* 1998 2.Nichols et al. *Cornea* 2000. 3.Pflugfelder et al. *Ophthalmology* 1990. 4.Lemp et al.*Am J Ophthalmol* 2011. 5.Schiffman et al. *Arch Ophthalmol* 2000.

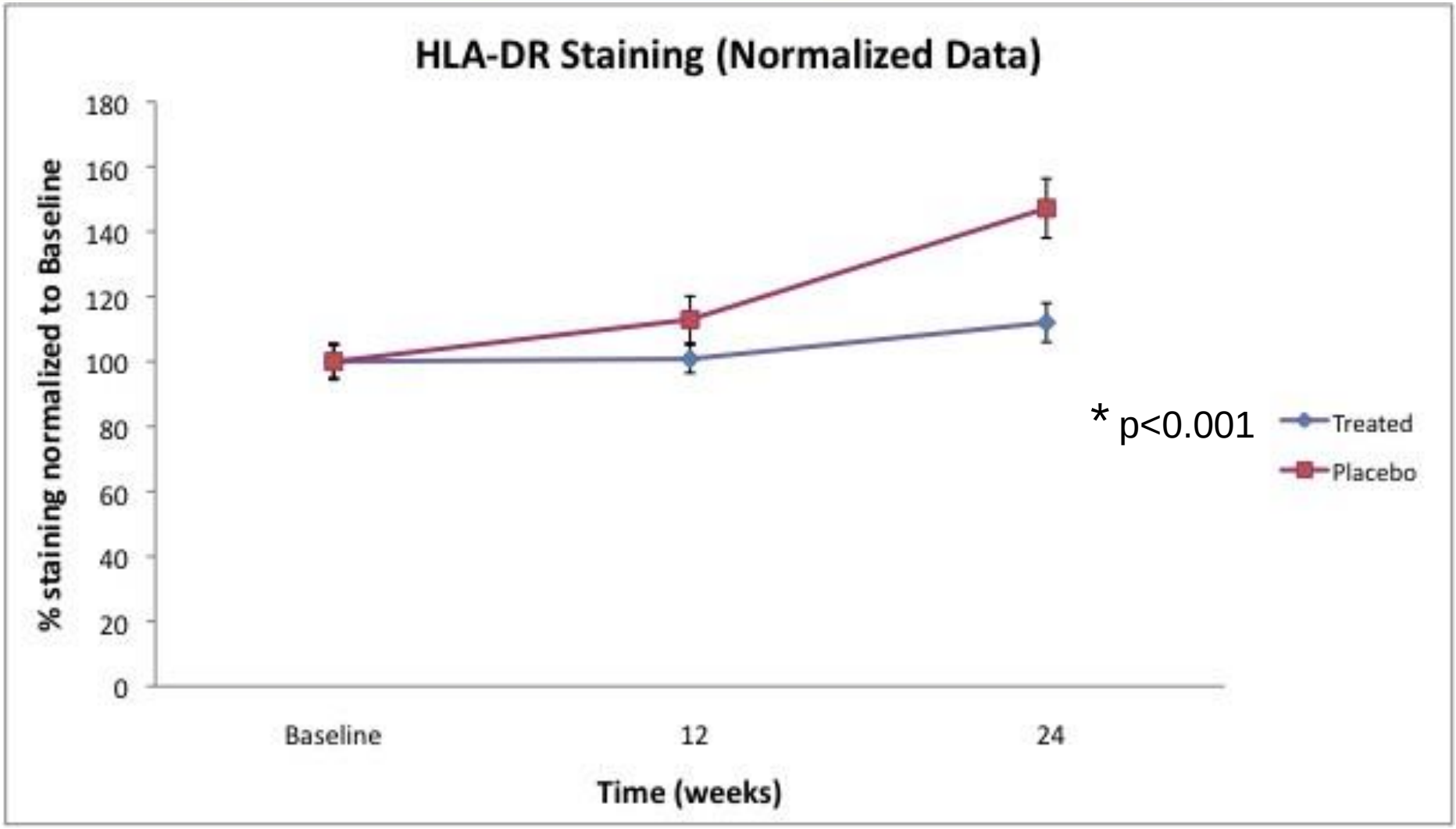
HydroEye® OSDI Results

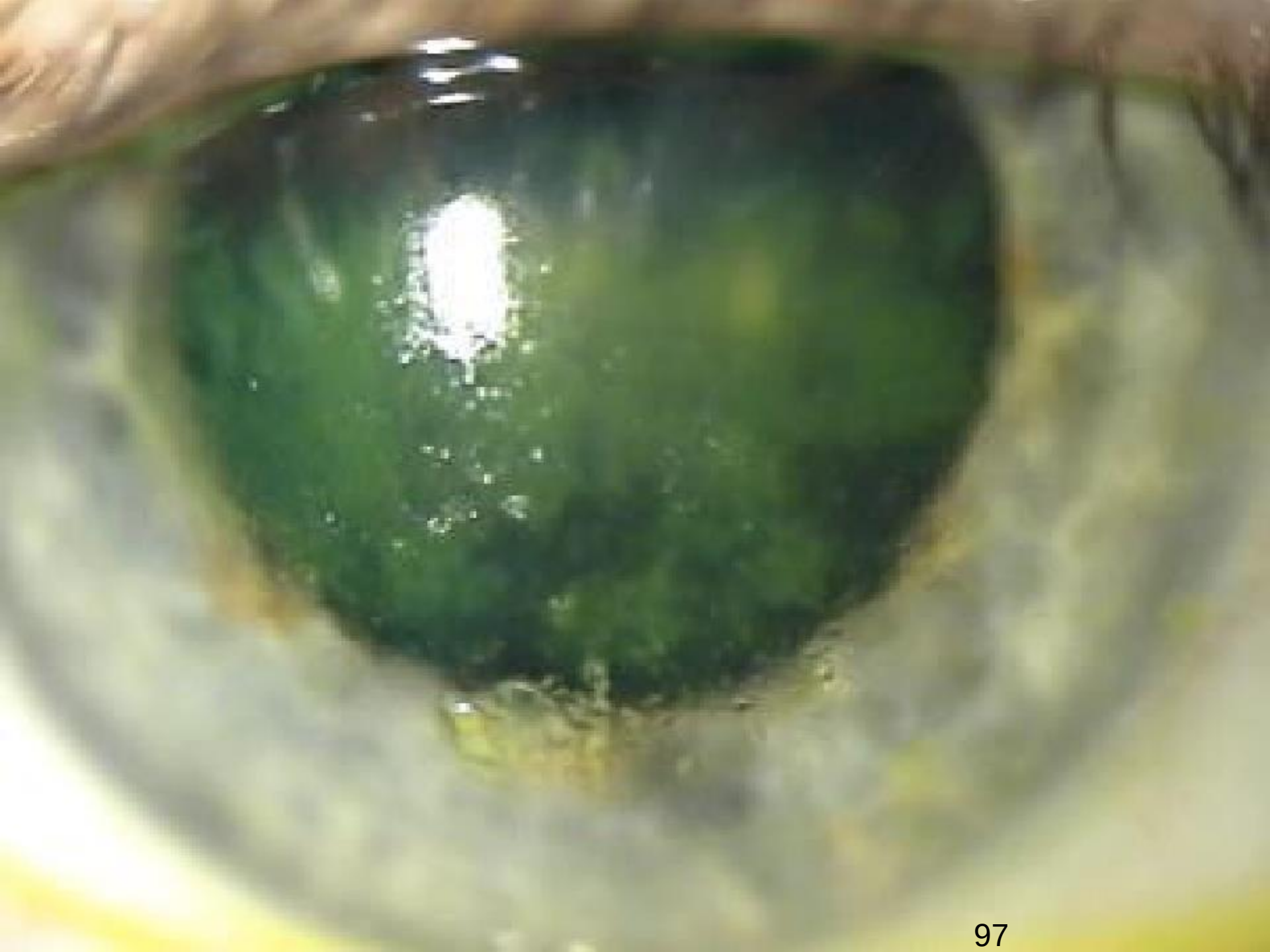


HLA-DR (green) and CD11c (red)



HLA-DR Impression Cytology Results





Focus on Dry Eye Prevalence

Cataract Surgery	77%
Penetrating Keratoplasty	60%
Lasik	27%
Glaucoma Surgery	8%
Blepharoplasty	26%

Trattler, ASCRS CME Supplement, 2013

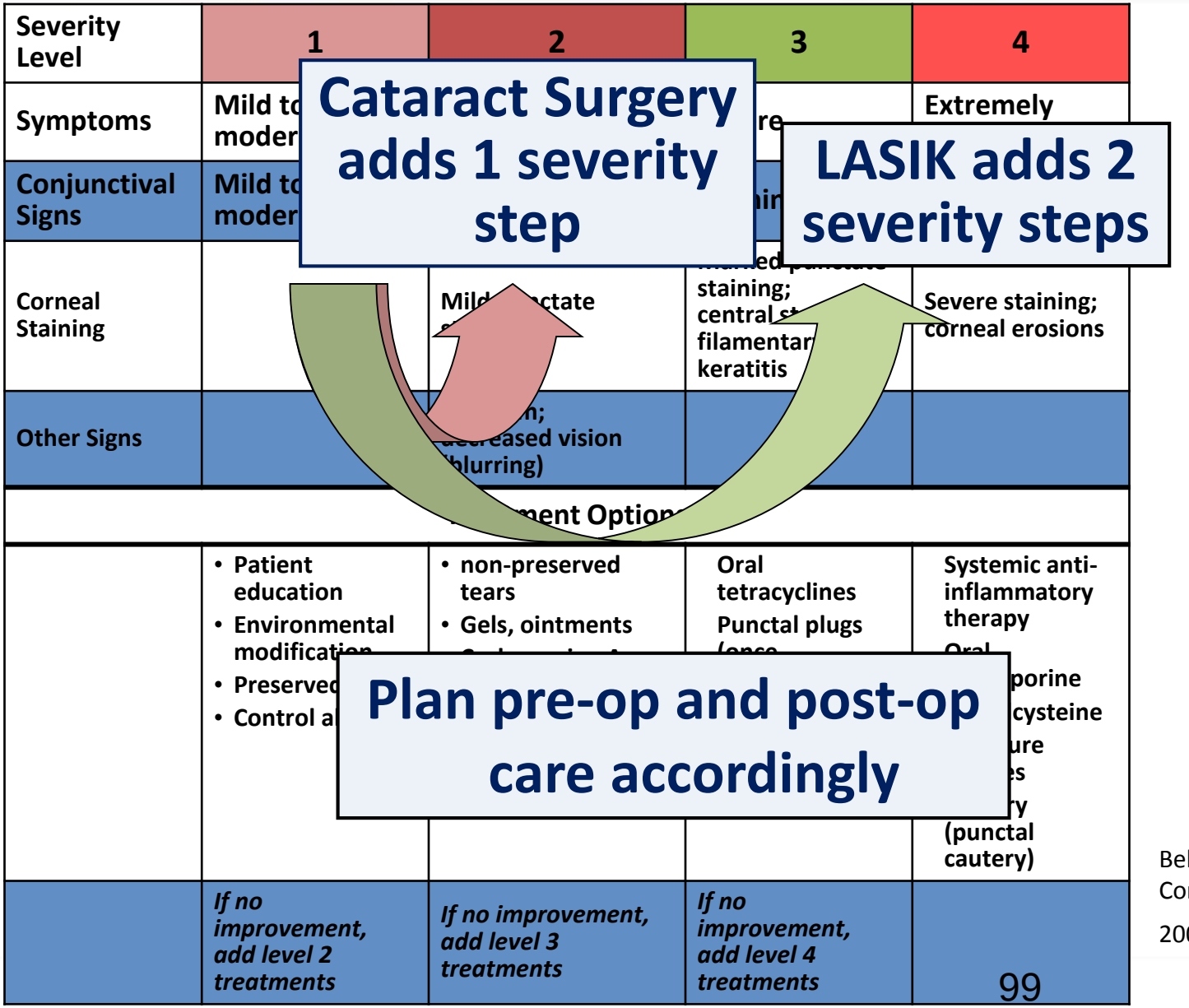
Sheppard, WCC, 2015

Azuma, BMC Research Notes, 2014

Leung, Journal of Glaucoma, 2008

Prischmann, JAMA Facial Plastic Surgery, 2013

Surgery Impacts Dry Eye



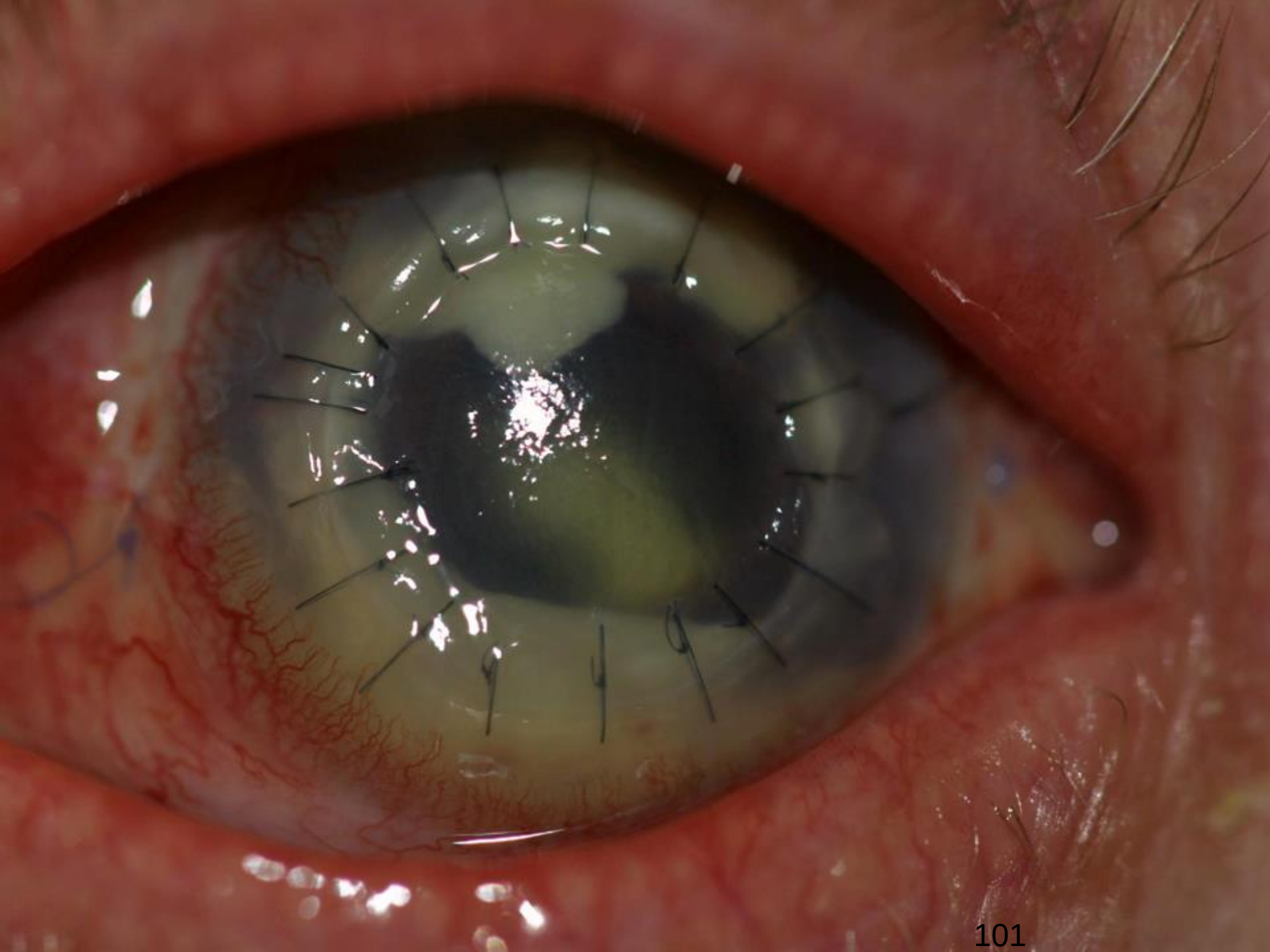
Severity Level	1	2	3	4
Symptoms	Mild to moder		re	Extremely
Conjunctival Signs	Mild to moder			
Corneal Staining		Mild ectate	staining; central st filamentar keratitis	Severe staining; corneal erosions
Other Signs		n; eased vision blurring)		
		ment Option		
	• Patient education • Environmental modificat • Preserved • Control a	• non-preserved tears • Gels, ointments	Oral tetracyclines Punctal plugs (once	Systemic anti-inflammatory therapy Oral porine cysteine ure es ry (punctal cautery)
	If no improvement, add level 2 treatments	*If no improvement, add level 3 treatments*	*If no improvement, add level 4 treatments*	

Cataract Surgery adds 1 severity step

LASIK adds 2 severity steps

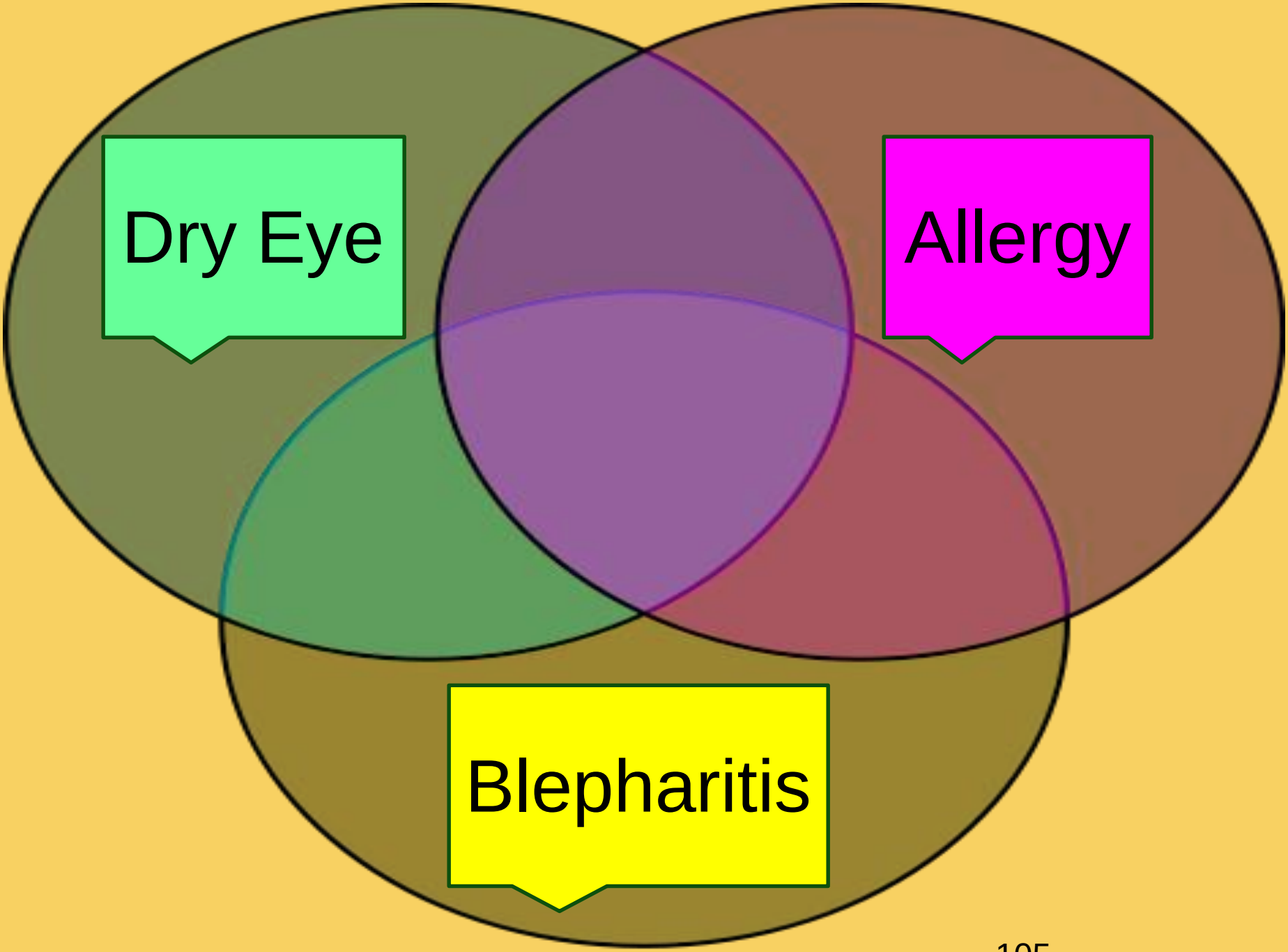
Plan pre-op and post-op care accordingly

Behrens A, et al. Cornea. 2006;25:900-7.



Calcific Band Keratopathy

No Magic Bullet: Dry Eye is a Highly Heterogeneous Disease

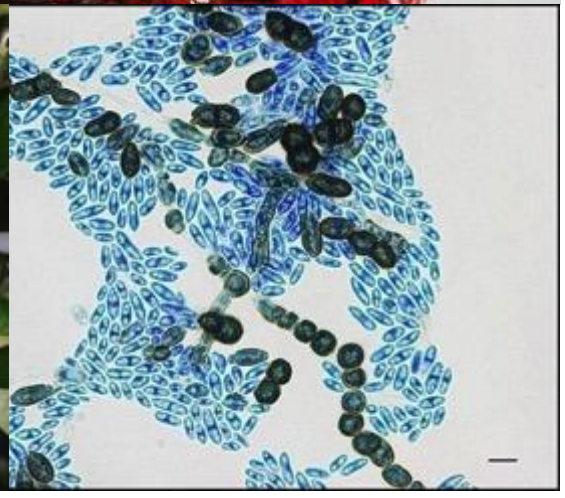

Dry Eye
Allergy
Blepharitis

Allergic Conjunctivitis

CUSTOM ALLERGENS SPECIFIC TO YOUR AREA





CUSTOM ALLERGENS SPECIFIC TO YOUR AREA

Allergens vary by geographic location.

Customized & Regionalized

A proprietary, FDA-approved, diagnostic test specific for ocular allergies.

VIRGINIA eye consultants

CUSTOM ALLERGENS SPECIFIC TO YOUR HOME

Rationale

Ocular Allergies affect about 20% of Americans.

Rationale

50% have concomitant Dry Eye Syndrome

Rationale

Over 30 million Americans have both eye disorders.

Allergic Conjunctivitis and Dry Eye Syndrome

Annals of Allergy, Asthma & Immunology
March 2012; 108(3); 163-6.
Milton Hom OD, Andrew Nguyen PhD,
Leonard Bielory MD

Most patients with “itchy eyes” consistent with AC also have dry eyes and redness. These results suggest that some symptomatic patients concomitantly have features of AC and DES.

Ocular Allergy Treatments

Current Treatment Modalities

Topical Antihistamines

The current treatment of choice for ocular allergies is topical antihistamines which typically are effective for the allergic component.

Neutriceuticals

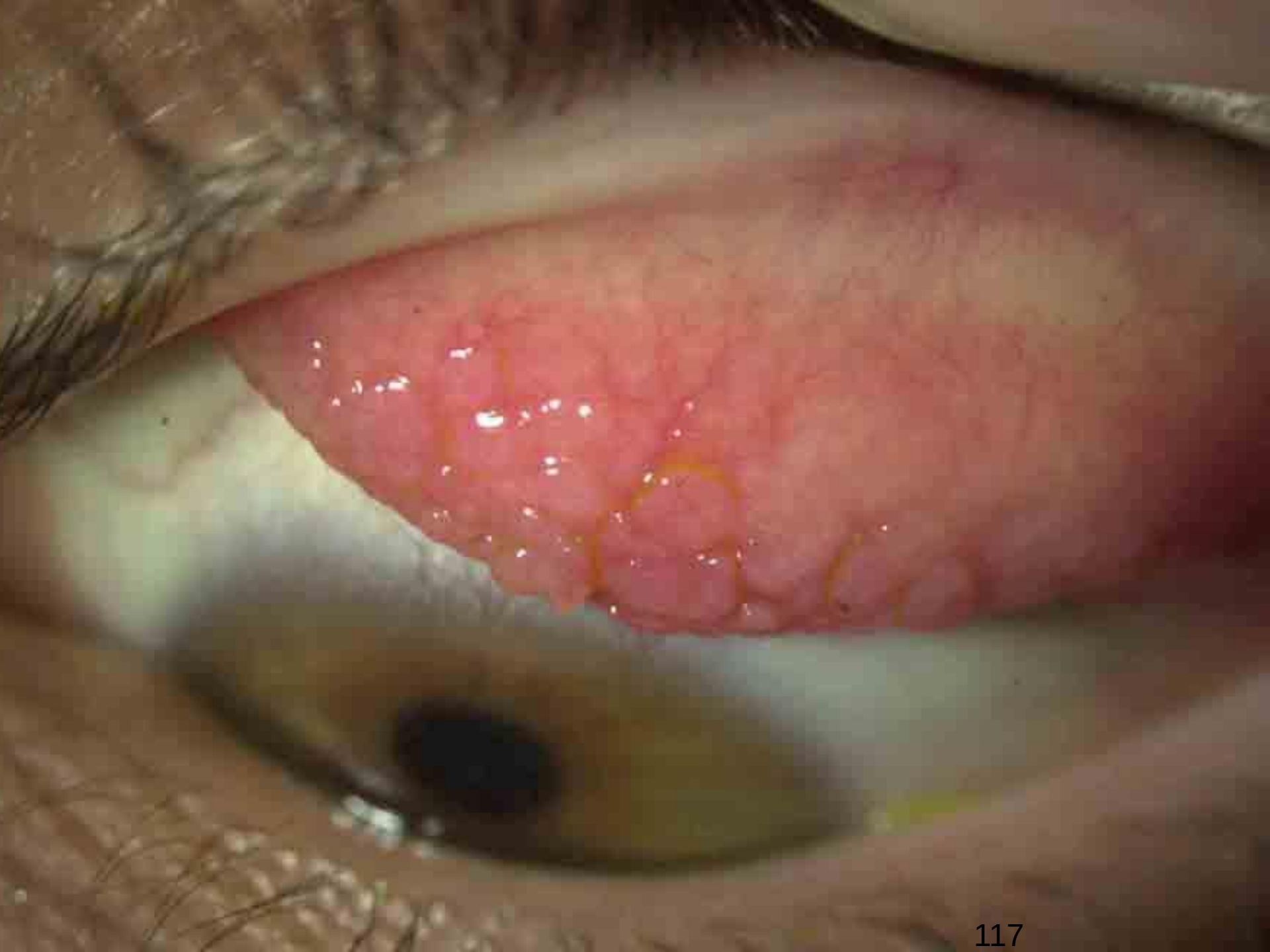
Allergy nutraceutical helps patients without the deleterious effects associated with Antihistamines. This success led to the development of the eye drop formula.

Exacerbating DES Symptoms

Unfortunately, these topical antihistamines exacerbate Dry Eye symptoms limiting their usefulness.

Ocular Allergy Complications

- Chronic Discomfort
- Foreign Body Sensation
- Pruritis & Epiphora (Itching & Tearing)
- Decreased Productivity
- Depression
- Contact Lens Intolerance
- Poor Surgical Predictability & Outcomes
- Inflammatory Keratitis



Allergy Intersects with Dry Eye

- Dry Eye Treatments (Restasis, Xiidra) are Ineffective for Ocular Allergy
- ADX-102 is Uniquely Positioned as a Unique MOA for safe long-term treatment of this growing patient cohort
- ADX-102 shows clinically relevant effects in the Phase IIb Allergy Trial *and*
- Clinical efficacy output is very encouraging in the Phase IIa Dry Eye Study

ADX-103 and a New Program in Retinal Disease

Susan Macdonald, PhD
Vice President, Research and Development
Aldeyra Therapeutics

A Novel Aldehyde Trap and a New Development Program in Retinal Disease

- ADX-103
  - Second-in-class aldehyde trap
  - Shown to have mechanism of action as ADX-102, but different structure
- ADX-103 for retinal disease
  - Like ADX-102, ADX-103 has shown activity in multiple pre-clinical models of ocular disease
    - Endotoxin-induced uveitis (intravitreal)
    - Macular degeneration (systemic)
    - Diabetic macular edema (intravitreal)

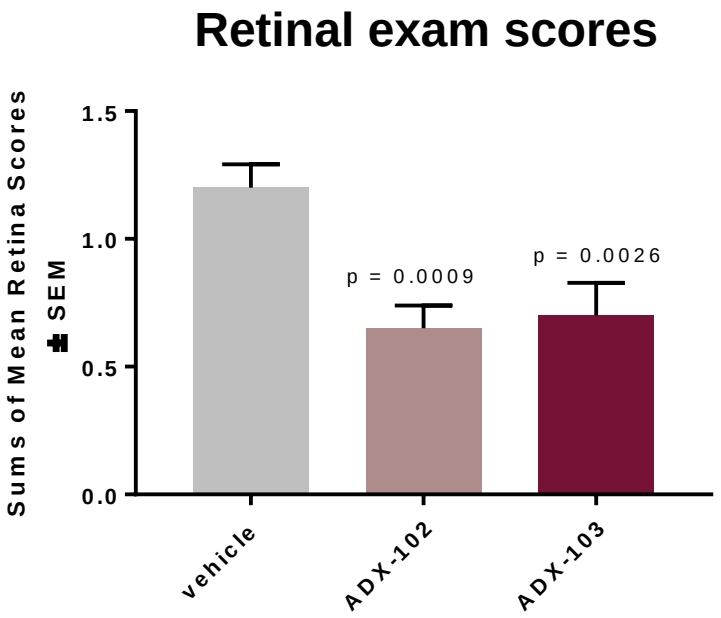
Uveitis: Aldehyde Traps Reduce Retinal Inflammation

Model: Ocular inflammation in rats induced by footpad injection of a bacterial endotoxin (LPS)

Disease-related aldehydes: Malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE)

Dosing: Single intravitreal dose; 25 µg/eye, one hour following LPS challenge

Results: ADX-102 and ADX-103 reduced retinal inflammation, as measured by retinal exam scores[1]



[1]Vasculopathy; retinal hemorrhage, exudate or detachment; choroidal hemorrhage, exudate or detachment

Macular Degeneration: Aldehyde Traps Reduce Formation of Toxic Retinal Metabolite A2E

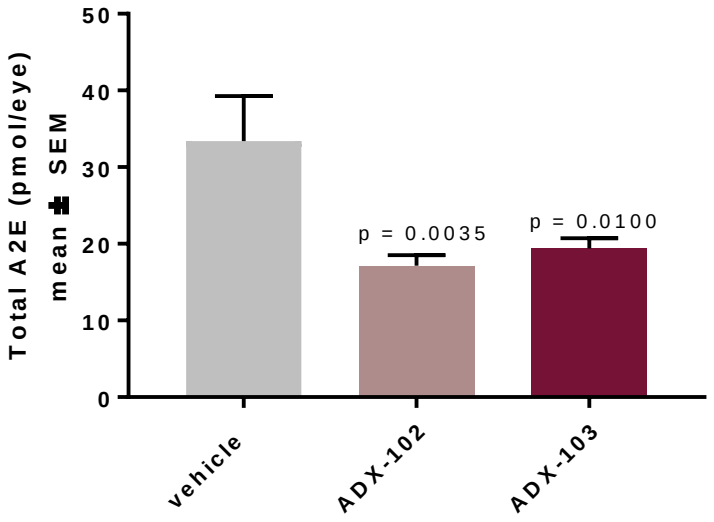
Model: Knockout mice that do not express ABCA4. ABCA4 transports all-*trans*-retinal to a location in the retina where it is converted to a non-reactive substance, preventing the accumulation of toxic by-products of the visual cycle, such as A2E, in the retina.

Disease-relevant aldehyde: Retinaldehdye (all-*trans*-retinal)

Dosing: 10 mg/kg, intraperitoneally, once daily for 56 days

Results: Both ADX-102 and ADX-103 significantly reduced the formation of A2E in the retina

A2E levels in abcr$^{-/-}$ mice



Diabetic Macular Edema: ADX-103 Blocks Diabetic Retinal Degeneration

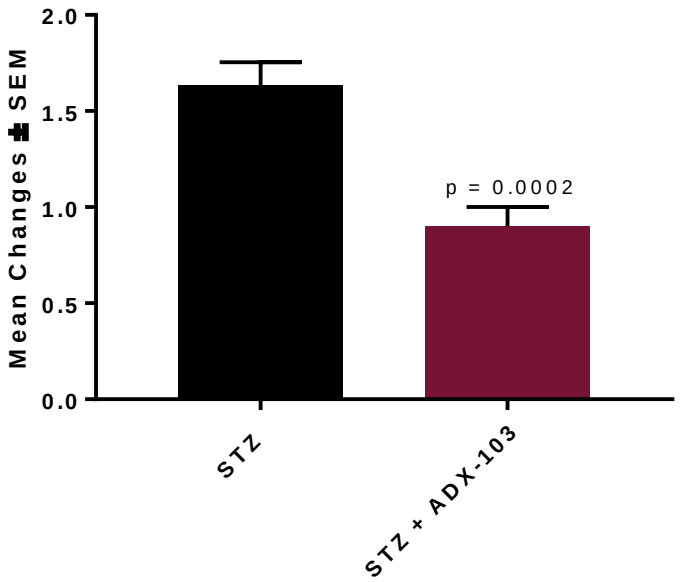
Model: Streptozotocin (STZ)-induced diabetes in rats. Retinal changes are monitored over time.

Disease-relevant aldehydes: Glyoxal and methylglyoxal

Dosing: Two single doses of ADX-103, intravitreally, over 29 days, after induction of diabetes

Results: Histopathology of the retina 29 days after the first dose of ADX-103 indicated that ADX-103 significantly reduced retinal thickness induced by diabetes.

Retinal thickness changes after two IVT doses of ADX-103

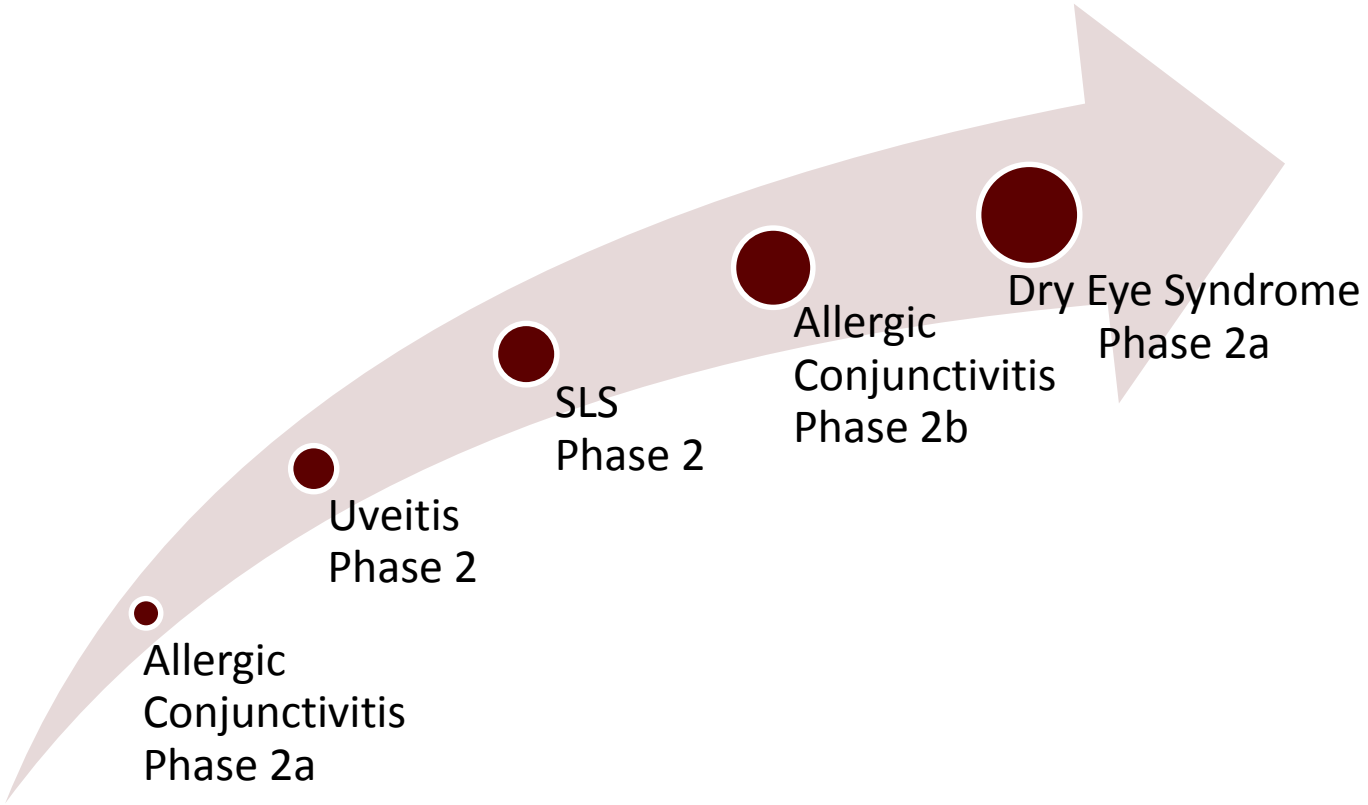


Scale:
1 = minimal microscopically visible changes
2 = mild microscopically visible changes
3 = moderate microscopically visible changes

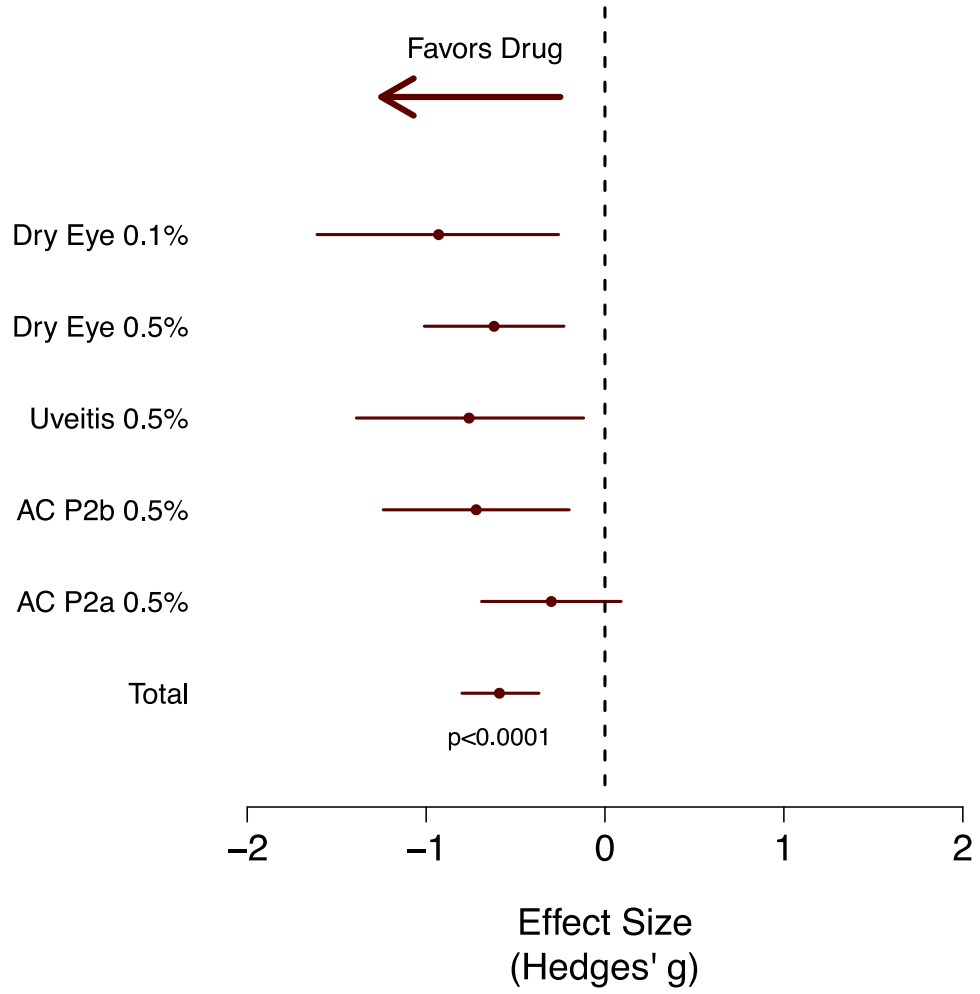
Clinical Trials Successes and Expected 2018 Clinical Milestones

David Clark, MD
Chief Medical Officer
Aldeyra Therapeutics

Five Positive Phase 2 Trials Completed Over 18 Months



Meta-analysis of ADX-102 Strongly Supports Drug Activity



p value is subject to change based on quality control analysis; between-group comparisons used where placebo control, otherwise within-group comparisons used; dry eye results based on ocular discomfort symptom score.

Expected 2018 Clinical Trial Milestones*

	Product Candidate	Phase	Milestone
Ocular Inflammation	Noninfectious Anterior Uveitis	Phase 3	Results 2H18
	Allergic Conjunctivitis	Phase 3	Initiation 1H18 Results 2H18
	Dry Eye Disease	Phase 2b	Initiation 1H18 Results 2H18
Inborn Errors of Aldehyde Metabolism	Sjögren-Larsson Syndrome (SLS)	Phase 3 (Derm, Part I)	Initiation 1H18 Results 2H18
	Systemic ADX-10X†	Phase 1-2 (SLS, Inflammation)	Initiation 2H18

*Pending regulatory agency discussions, additional non-clinical data, and other factors, which may not be in Aldeyra's control
†Timing contingent on product candidate selection and additional non-clinical data