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Melanocortin Agonists for Ocular Diseases

May 21, 2021

Agenda

Introduction	
Speakers	
Corporate update	
Introduction to the Melanocortin System	Andrew W. Taylor, Ph.D.
Palatin Melanocortin Overview	John H. Dodd, Ph.D.
Dry Eye Disease & PL9643 Phase 2 Data	Eric Donnenfeld, MD
Melody 1: PL9643 Phase 3 Clinical Trial	George Ousler
Retinopathy Preclinical data & Clinical Opportunity	Peter Kaiser, MD
Question & Answer	All Speakers
Concluding Comments	

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Introduction to Speakers

Guest Speakers

Andrew W. Taylor, Ph.D.	Associate Dean of Research & Professor of Ophthalmology Boston University School of Medicine
Eric Donnenfeld, MD	Clinical Professor of Ophthalmology New York University School of Medicine
George Ousler	Senior Vice President Anterior Segment, Ora, Inc.
Peter Kaiser, MD	Staff Member Vitreoretinal Facility, Cole Eye Institute Department of Ophthalmology Cleveland Clinic

Palatin Speakers

Carl Spana, Ph.D.	CEO & President
Stephen T. Wills, CPA, MST	CFO, COO
John H. Dodd, Ph.D.	Senior Vice President, Research
Robert Jordan	Senior Vice President, Program Operations
Paul Kayne, Ph.D.	Executive Director, Biological Sciences
Bruce Stouch, Ph.D.	Director, Biostatistics & Clinical Epidemiology, The Philadelphia College of Osteopathy Pres. & Principal Biostatistician, BCS Statistical Solutions, LLC

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Development Programs

Clinical Pipeline

Melanocortin Receptor Programs	Pre-clinical	Phase 1	Phase 2	Phase 3	NDA Submission	FDA Approval	Status/Next Steps
Vyleesi® (bremelanotide) Hypoactive Sexual Desire Disorder							FDA Approval 6/21/2019. Licensees: Fosun (China, Taiwan, HK, Macau) and Kwangdong (S. Korea) Seeking ROW licenses
PL9643 MCR Agonist Dry Eye Disease							Phase 2 Dry Eye 1Q2020 Positive Data Obtained 4Q2020 Initiate Phase 2/3 1H2021 Phase 2/3 data 1H2022
PL9643 MCR Agonist Second Front of the Eye Indication							Evaluating options
MCR Agonist Diabetic Retinopathy Non-Infectious Uveitis							File IND for DR/DME 2H2021
PL8177 MC1R Agonist (Oral) Inflammatory Bowel Disease							Initiate ulcerative colitis Phase 2 in 1H2021. Ulcerative colitis Phase 2 data 1H2022

Natriuretic Peptide Receptor Programs	Pre-clinical	Phase 1	Phase 2	Phase 3	NDA Submission	FDA Approval	Status/Next Steps
PL3994 NPR-A Cardiovascular Disease							Entering Phase 2a clinical trial supported by a grant from the American Heart Association in 2H2020
PL5028 NPR-A/C Agonist Cardiovascular and Fibrotic Diseases							Complete preclinical work Evaluate options

Source: Company Filings

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FDA Approved Vyleesi®

Helping Premenopausal Women with Hypoactive Sexual Desire Disorder (HSDD)

Improvements to Commercial Infrastructure

- Renegotiated supply agreements
- Realigned Specialty Pharmacies
  - Added KnippeRx
  - Improved PA process
  - Streamlined HCP and patient experience
- Changed Telemedicine partner
- Increased patient access
  - ~75% covered lives / ~50% commercial formularies
- Initiated geotargeted digital marketing program

Recent (3/31/21) Quarter Results

- Prescriptions up 24%
- Gross Vyleesi® sales up 89%
- Net revenue up 154%

Licensing Overview

- Licensed in China (Fosun) and S. Korea (Kwangdong)
- Active discussions for U.S and multiple other regions

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Financial Snapshot

Financial Highlights as of March 31, 2021	
Cash and Cash Equivalents	$68.6 million
Working Capital	$69.4 million
No Debt	

Summary Capitalization as of March 31, 2021	Common Shares and Equivalents
Common Stock	230.1 million shares
Preferred	0.1 million shares
Warrants	12.6 million shares
Options	19.8 million shares
RSUs	11.6 million shares
Fully Diluted Shares	274.2 million shares

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What are Melanocortins?

Investor Day

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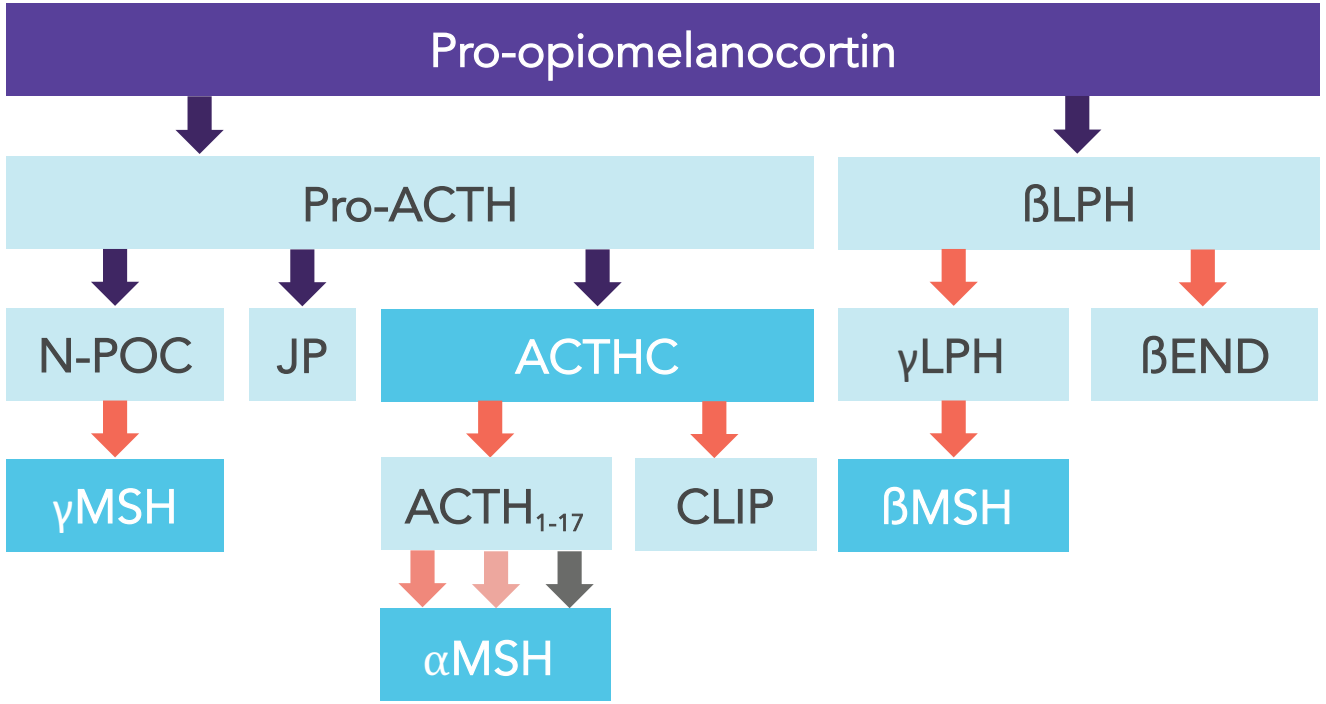
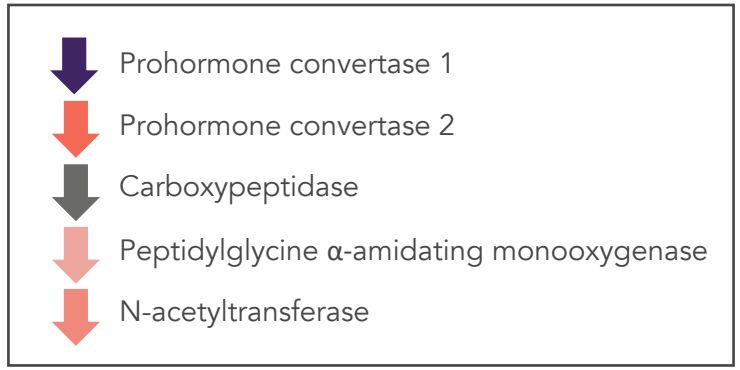
Melanocortin Neuropeptides





ACTH	SYSMEHFRWGKPVGKKRRPVKVYPNGADDESAEAFPLEF
α-MSH	Nac-SYSMEHFRWGKPV-NH2
ß-MSH	DEGPYRMEHFRWGSPPKD
γ-MSH	KYVMGHFRWDRF-NH2

Hypothalamus
Macrophages
Retinal Pigment Epithelial cells

Patel HB, Montero-Melendez T, Greco KV, Perretti, M. Melanocortin receptors as novel effectors of macrophage responses in inflammation. *Front Immun.* 2011;2:41.

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Melanocortin Receptors

MC1r

- α-MSH = ACTH > ß-MSH > γ-MSH
- Skin, Melanocytes, Keratinocytes, Endothelial cells, Mucosal cells, Adipocytes, Chondrocytes, Osteoblasts, Macrophages, Monocytes, Dendritic cells, Mast cells, Neutrophils, T cells, B cells

MC2r

- ACTH only

MC3r

- γ-MSH > ACTH = α-MSH = ß-MSH
- Hypothalamus, Macrophages, Monocytes, Dendritic cells, T cells, B cells, CNS

MC4r

- α-MSH = ACTH > ß-MSH > γ-MSH
- Hypothalamus, Dendritic cells, Osteoblasts, CNS

MC5r

- α-MSH > ACTH = ß-MSH >> γ-MSH
- Exocrine glands, Sebocytes, Macrophages, Dendritic cells, Mast cells, Chondrocyte, T cells, B cells, NK cells, CNS

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Activity of Melanocortins

- **Pigmentation**
  - Stimulation of melanogenesis and the modulation of proliferation of melanocytes and melanoma cells
  - MC1r is a major determinant of mammalian pigmentation
- **Metabolism**
  - Complement of leptin in the endocrine circuit, regulating bodyweight, food intake, and metabolic rate
  - α-MSH can decrease bodyweight, weight gain, and food intake in mice with diet-induced and genetic obesity
- **Neurobehavior**
  - Induced anxiolysis and anxiety-like behavior
  - Aggression control
  - MC4r, MC5r
- **Steroidogenesis**
  - Hypothalamic – pituitary – adrenal axis
  - ACTH through MC2r of the adrenal cortex
- **Other Roles:**
  - Through MC5r involved in the central control of LH release
  - Suppresses the synthesis of collagen types I, III, and V and down-regulates the secretion of procollagen type I C-terminal peptide (PICP) in human dermal fibroblasts
  - Exocrine gland function (MC1r, MC5r)

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Melanocortins and Immunobiology

- Suppression of endotoxin induced-inflammation (monocytes and neutrophils)
- Suppression of CHS
- Induction of MC1r expression and α-MSH production in macrophages (self-sustaining regulatory loop)
- Induction of suppressor APC
- Suppresses phagosome maturation (altered antigen presentation)
- APC that converts effector T cells into Treg cells
- Induction of Treg cells

<u>Suppression of:</u>

- Septic shock
- Uric crystal-induced arthritis
- Adjuvant-induced arthritis
- Experimental autoimmune encephalomyelitis
- Experimental allograft rejection
- Experimental autoimmune uveitis

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Effects of Glucocorticoids and α-MSH on the Eye

	Glucocorticoid	α-MSH
Immune effects	• Suppresses proinflammatory signals • Suppresses immune cell activity	• Suppresses proinflammatory signals • Promotes production of anti-inflammatory cytokines • Induces suppressor antigen-presenting cells • Induces activation of regulatory T cells • Natural regulator of immunity in healthy eyes
Optic nerve effects	• Indirect damage of optic nerve due to increased intraocular pressure • May sensitize nerve cells to disease-induced apoptosis	• Transiently lowers intraocular pressure • Can protect neuronal cells from damage
Adverse effects	• Causes cataracts • Induces increased intraocular pressure and glaucoma • Many other adverse events	• No known adverse events

Clemson CM, Yost J, Taylor AW. *Ocul Immunol Inflamm.* 2017;25:179-189. PMID:26807874.

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What Role do Melanocortins Have in Ocular Immunobiology?

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What Is Ocular Immune Privilege?

- The result of integrated biological systems (neural, immune, and visual) that exist within a blood-barrier with no direct lymphatic drainage
- A tissue site that affords prolonged allograft survival
- An evolutionary adaptation of an organ that needs to minimize the collateral damage of inflammation and infection to preserve function
- Attempts to dominate immune responses to promote immune tolerance

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Why Study Immune Privilege?

Understanding the mechanisms of ocular immune privilege provides us with insight into what is necessary to have a healthy ocular microenvironment, along with potential biomarkers of health and therapeutic efficacy, and to identify new, well-tolerated molecules for ocular therapy.

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Active Mechanisms—Soluble Factors

Factor	Activity
TGFß2	Suppresses activation of T cells, NK cells, MØ, promotes tolerance-inducing APCs
a-MSH	• Converts IFN-producing T cells into regulators • Inhibits PMN activation, works with NPY to induce suppressor MØ • Antagonizes LPS, IL-1, TNF-mediated inflammation
VIP, Somatostatin	Inhibits T cell activation
CGRP	Inhibits LPS activation of MØ, suppresses APC promotion of TH1 differentiation
Thrombospondin	Promotes activation of TGFß, promotes MIP-2 secretion, suppresses IL-12, CD40 expression by APCs
MIF	Inhibits NK cell killing
IL-1r**a**	Inhibits IL-1**a**,ß pro-inflammatory effects
sCD46,55,59	Inhibit complement activation
sCD95L	Suppresses PMN recruitment and activation
PEDF	Suppression of LPS-stimulated IL-1 and TNF**a** production by MØ
NPY	Works with **a**–MSH to induce suppressor MØ

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Active Mechanisms—Membrane-Bound Factors

Factor	Activity
Fas Ligand	Induces apoptosis in T cells and neutrophils
CD86	Inhibits T cell activation
DAF	Inhibits complement cascade
Galectin-1	Inhibits T cell activation
MHC Class 1b	Inhibits NK and CTL killing
TRAIL	Induces apoptosis in MØ and neutrophils

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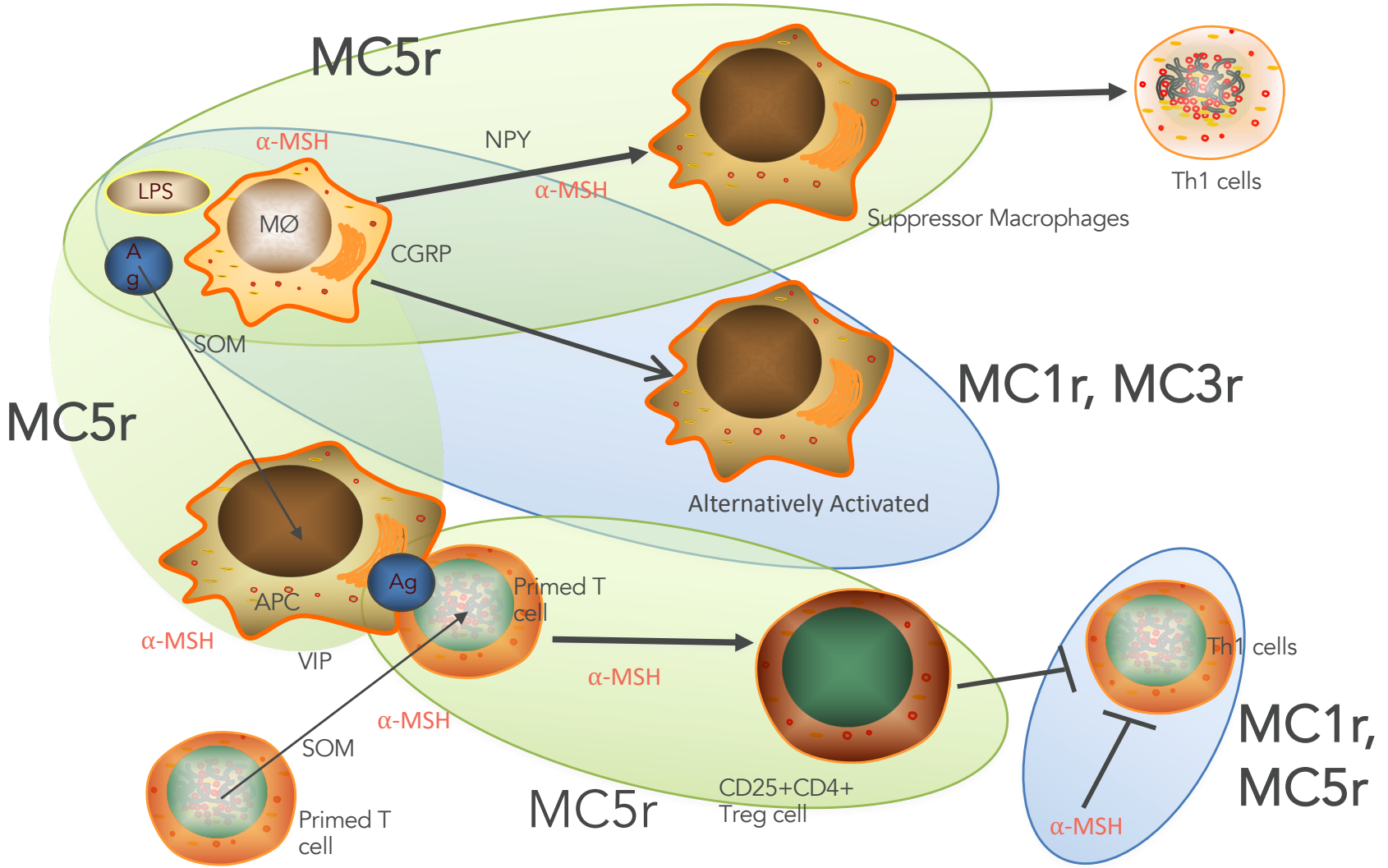
Role of Melanocortin Receptors and α-MSH in Ocular Immune Privilege



Clemson CM, Yost J, Taylor AW. *Ocul Immunol Inflamm.* 2017;25:179-189. PMID:26807874.

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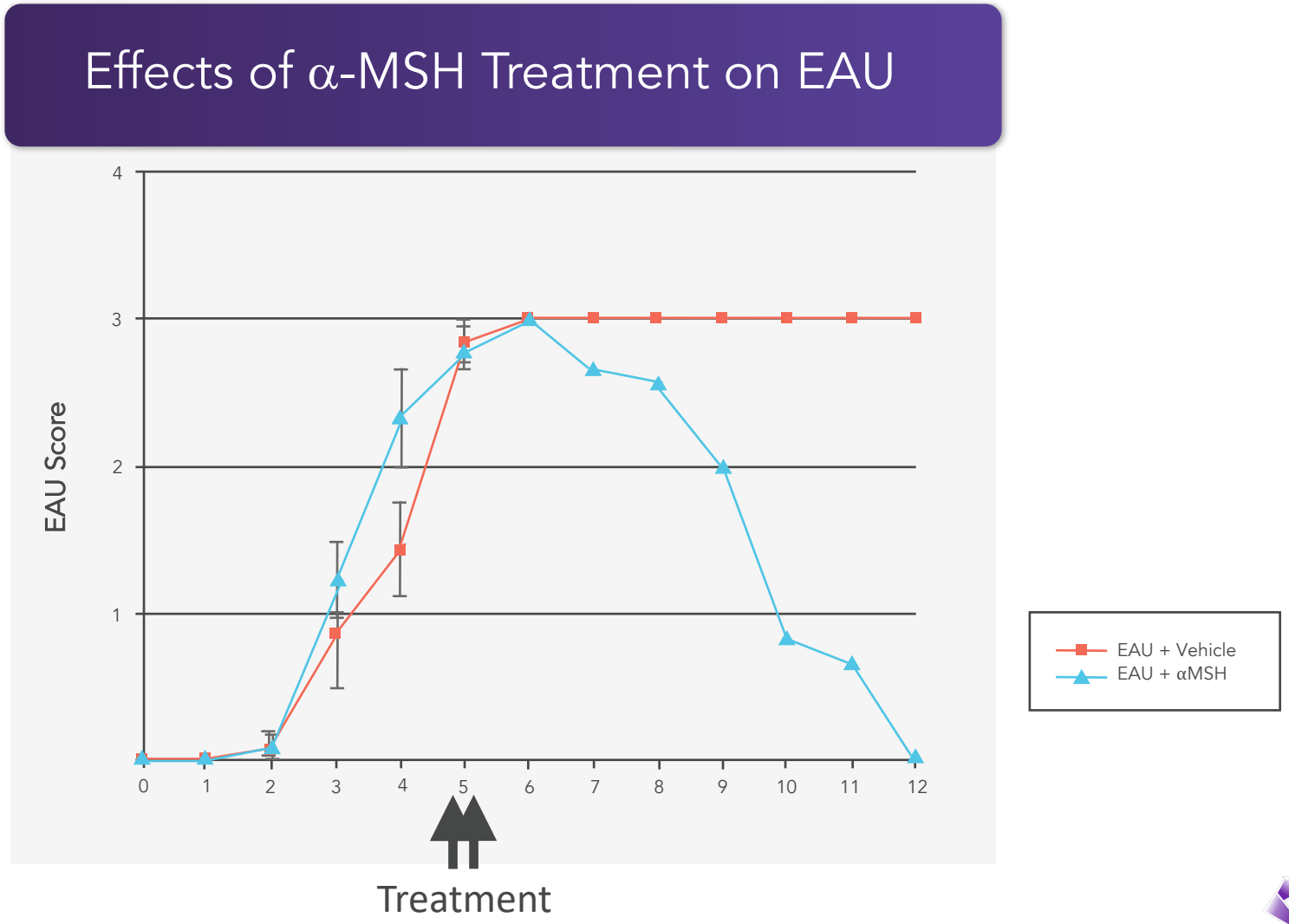
Effects of α-MSH Treatment on EAU



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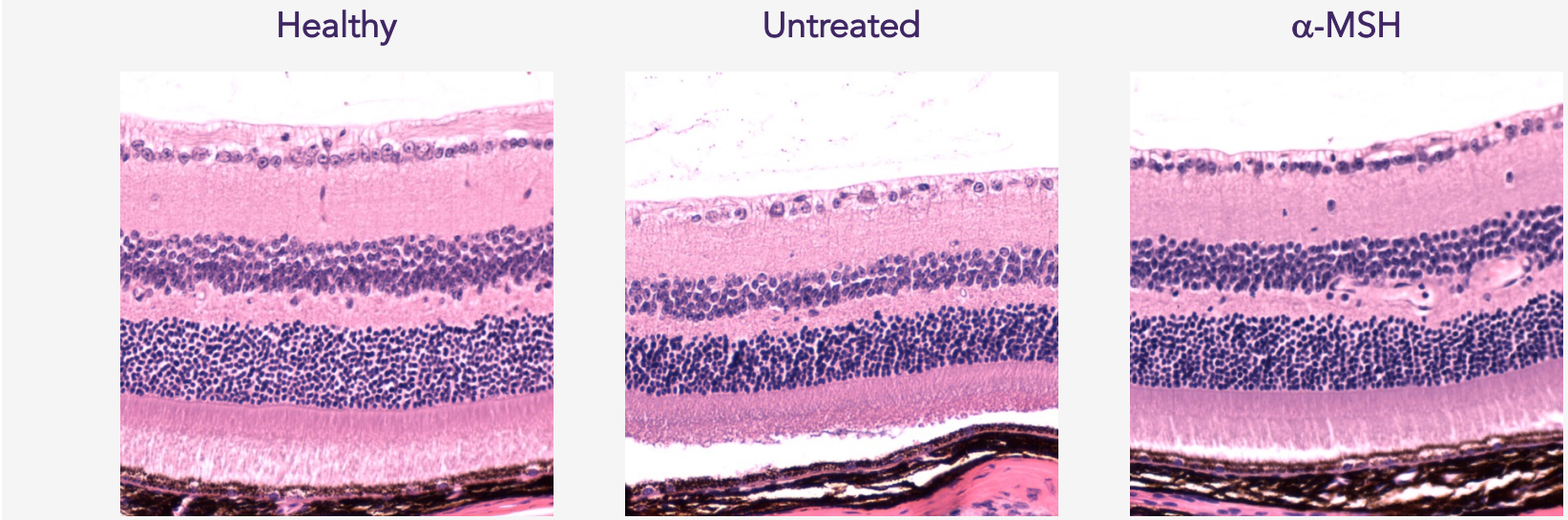
Retinal Histology of α-MSH treated EAU



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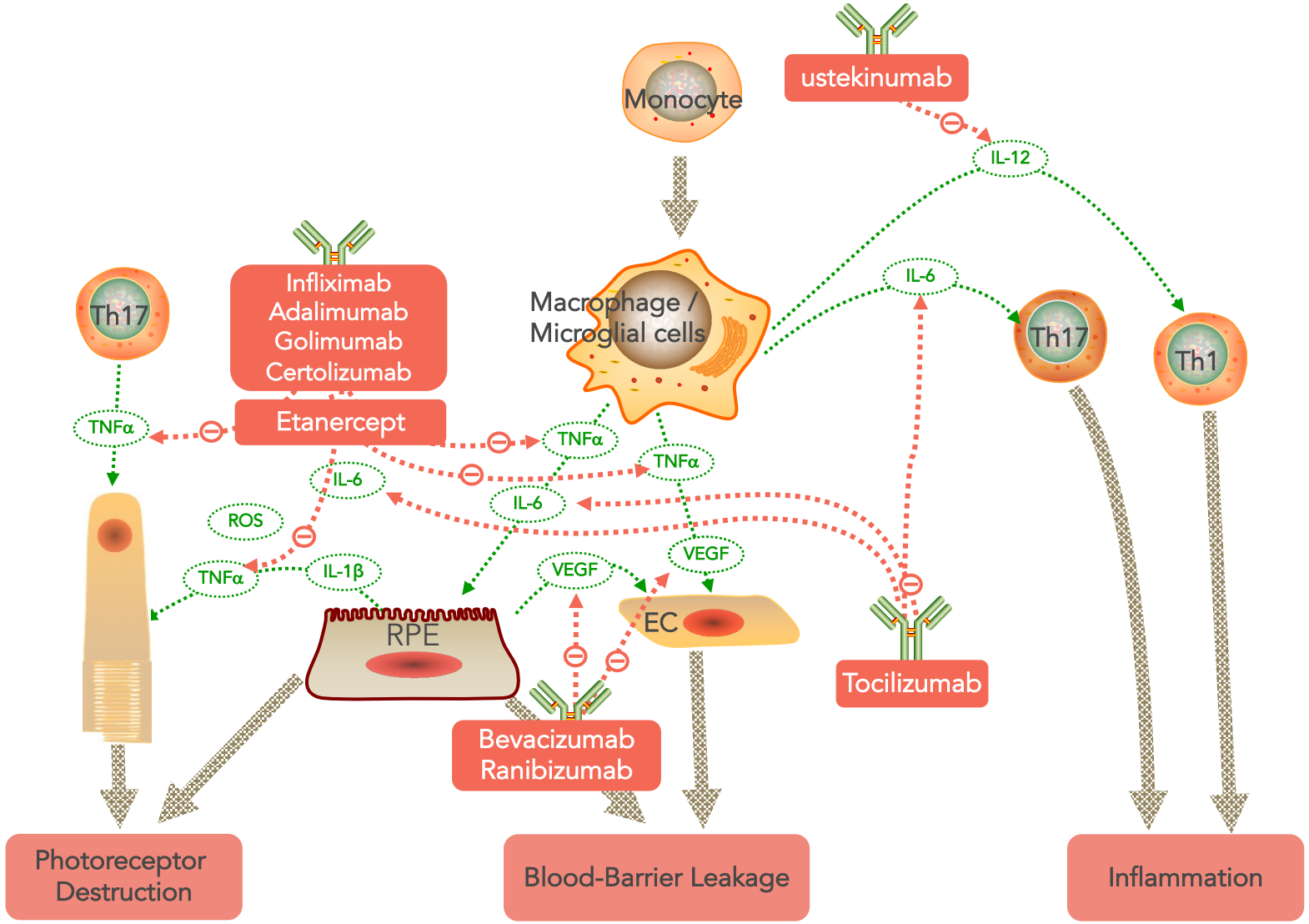
Drug Targets in Uveitis



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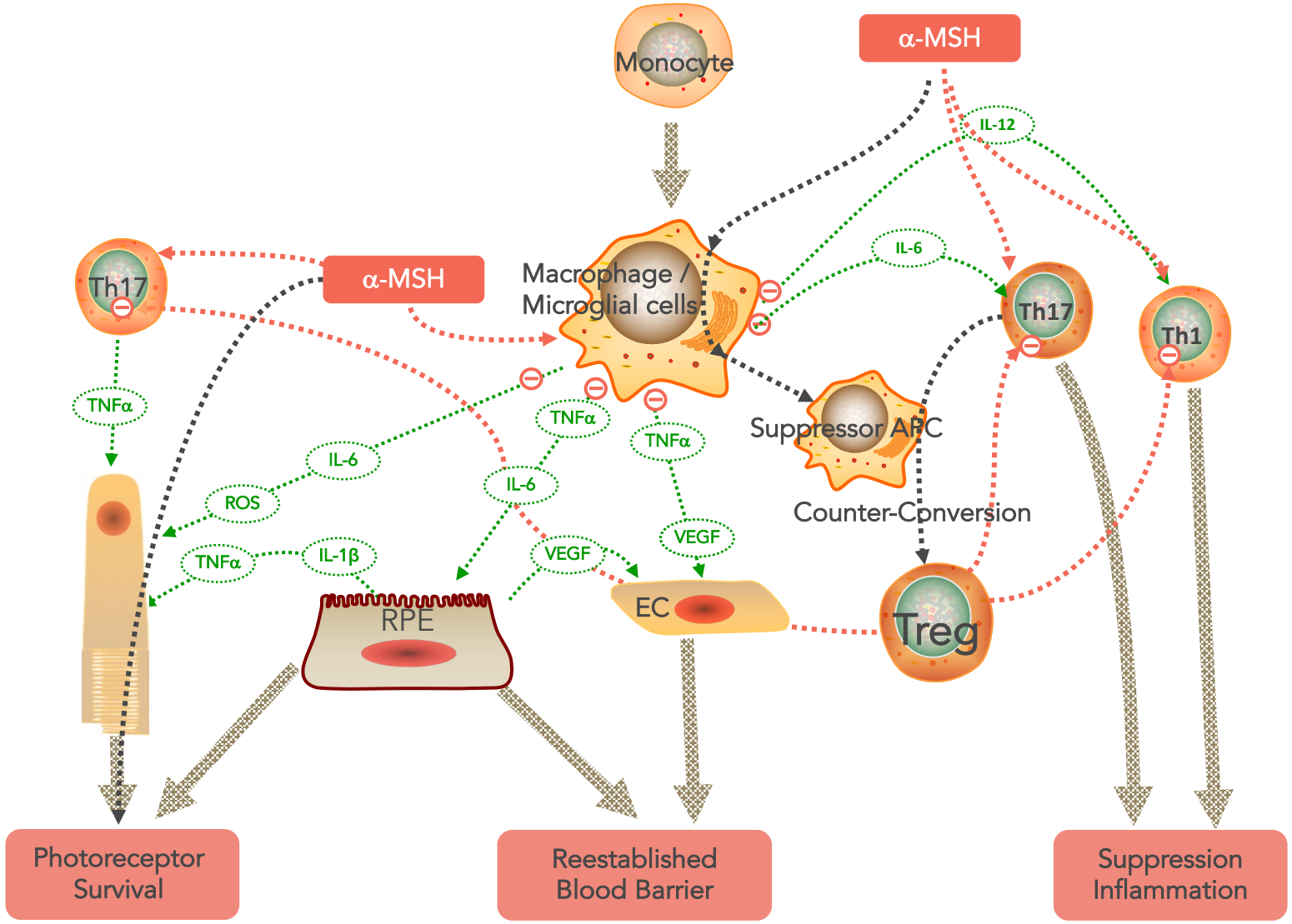
α-MSH Targets in Uveitis
Ocular Microenvironment Becomes Immunosuppressive?



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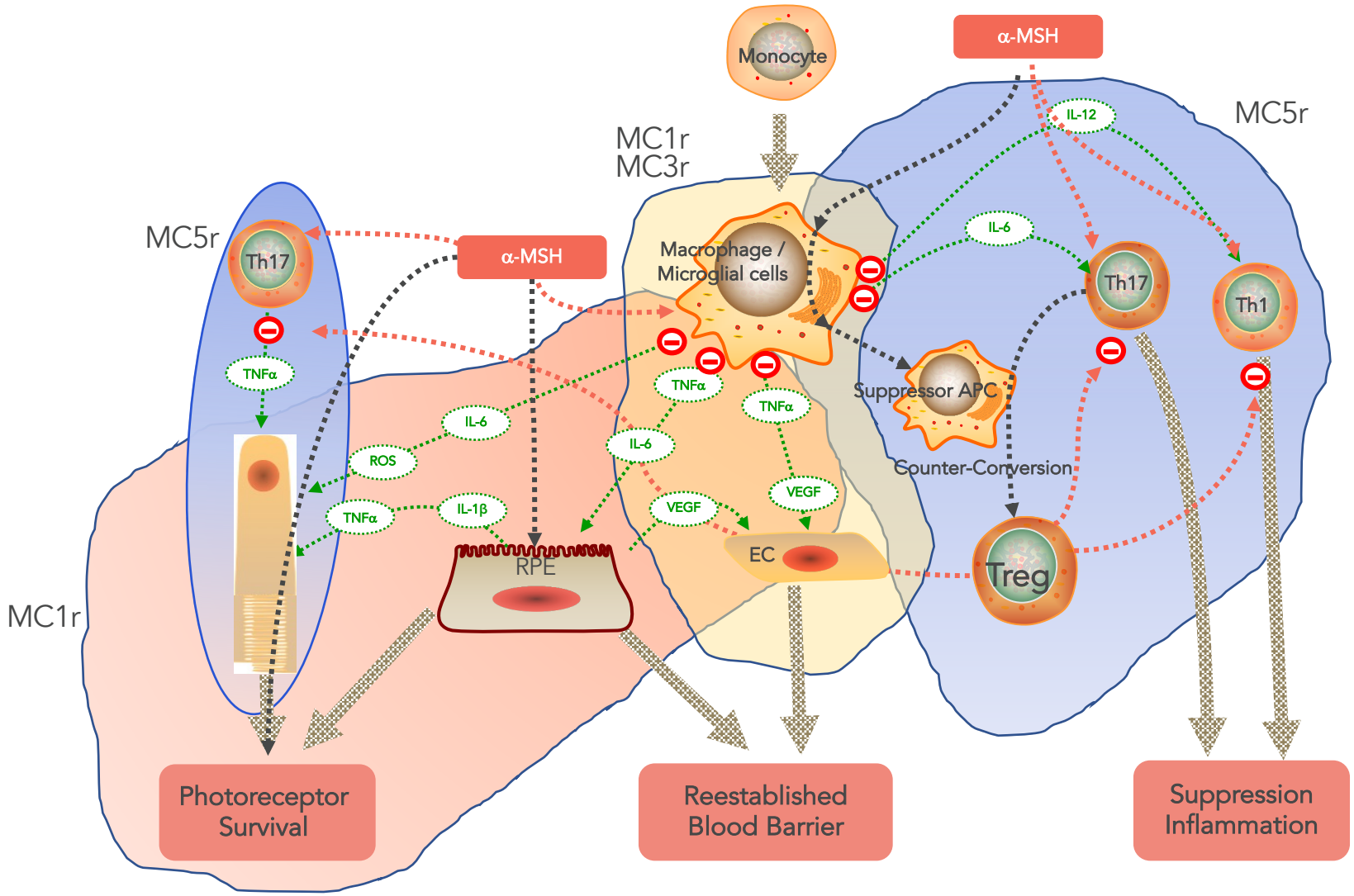
α-MSH Targets in the Diseased Ocular Microenvironment



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Conclusions

- α-MSH peptides are highly effective in suppressing EAU
- Stimulating the melanocortin receptors is not just an antagonism of pro-inflammatory signals but a change in cellular behavior (contrast with steroids and biologics)
- The melanocortin induction of regulatory immunity could be a pathway in humans with autoimmune disease

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Investor's Day

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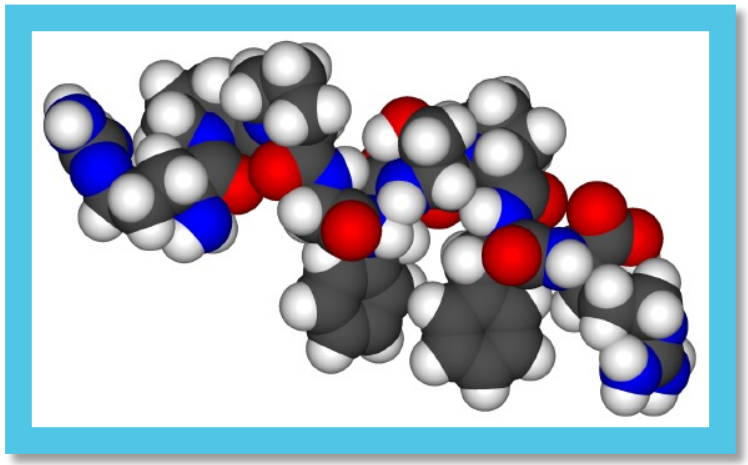
Key to Success – The Right Compounds for the Right Indications

Melanocortin System Inflammatory Disease Potential

?

Commercially Successful Product



- The most acceptable route of administration
- Optimal potency/selectivity/efficacy
- Excellent safety profile
- Clear advantage over existing/future therapies

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Two Compounds – Ulcerative Colitis and Dry Eye Disease

PL8177 OCD (oral, colon delivery)

- Selective MC1r agonist for Ulcerative Colitis
- Oral route of administration
- Local site of action – no systemic absorption
  - No safety issues identified
  - No tolerability issues identified
- Preclinical efficacy equal to or superior to 5-ASA's and steroids

PL9643 (topical drops)

- Pan Melanocortin agonist for Dry Eye Disease
- Topical drops
- Local site of action – no systemic absorption
  - No safety issues identified
  - No tolerability issues identified
- Preclinical efficacy equal to Cyclosporin A
  - Faster onset of action clinically

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MC1r Selective PL8177 OCD Properties

Superior potency and stability to the endogenous ligand – α-MSH

Potency

- Cellular in vitro assays demonstrate 640 times more potency (14 picomolar) than the endogenous ligand
- α-MSH in human cells – allows practical dosing levels

Selectivity

- Inactive at MC2r, MC3r, and MC5r and 6,000 times more potent at MC1r than MC4r
- No activity at 72 various non-melanocortin targets at 1,000,000X the concentration of MC1r activity

Stability

- Cyclic peptide structure inhibits proteolysis and degradation, significantly more stable than α-MSH, results in prolonged tissue engagement

Distribution

- Low membrane permeability maintains high levels at colon lumen surface, avoids systemic uptake

Safety

- Even when administered systemically, PL8177 has no off-target effects in preclinical and human studies

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Pan Melanocortin Agonist PL9643 Properties

Superior potency and stability to the endogenous ligand – α-MSH

Potency

- More potent in cellular in vitro functional assays compared to α-MSH (EC_{50}, nanomolar, nM)

	PL9643	α-MSH	fold greater potency
MC1r	0.13	9.0	69
MC2r	Inactive	Inactive	---
MC3r	0.022	8.0	360
MC4r	0.014	16	1100
MC5r	0.39	370	950

- High potency of PL9643 allows topical solution to be extremely dilute (1 microgram in 1 mL of vehicle)
- Pan agonism allows engagement of all melanocortin receptors that could potentially have a desirable effect

Stability

- Cyclic peptide structure inhibits proteolysis and degradation, significantly more stable than α-MSH, results in prolonged engagement of corneal and conjunctival tissues

Distribution

- Low membrane permeability maintains high levels at corneal and conjunctival tissue, avoids systemic uptake

Safety

- No systemic levels detected in preclinical animal testing or human clinical trials
- Low drug concentration translates into no preclinical or clinical adverse events or tolerability issues

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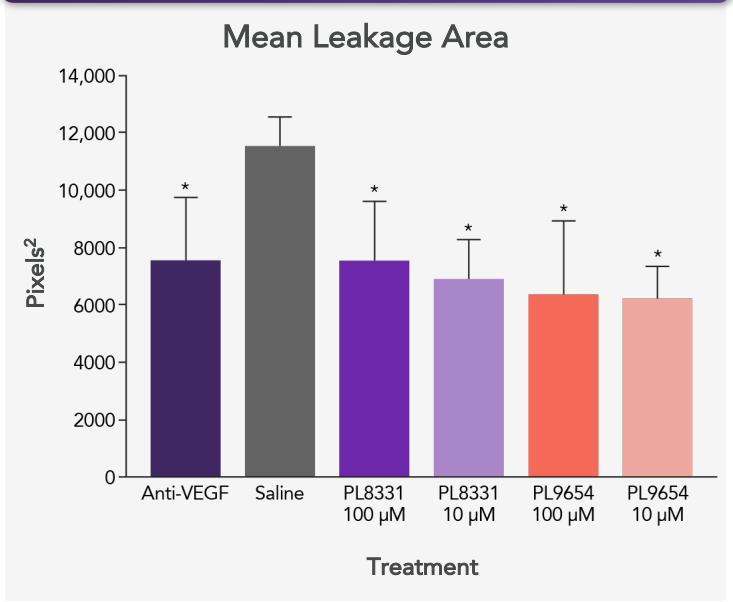
Back of the Eye Research Progress – PL9654

- Palatin melanocortins have been evaluated in several animal models of retinal disease. We have observed effects equal to anti-VEGF therapy
- Progress is being made on identifying the formulation and route of administration for advancement into development

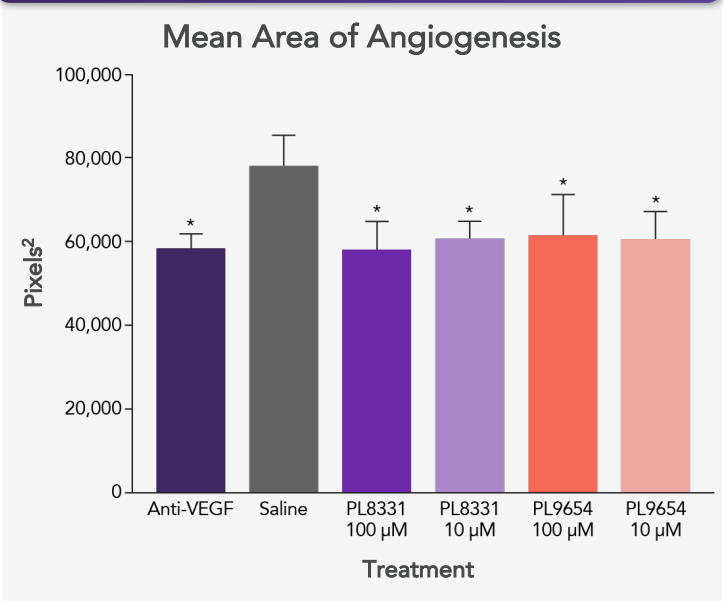
Figure 6. Areas of Leakage Measured Using Fundus Fluorescein Angiography



VEGF, vascular endothelial growth factor.

*$P \leq 0.05$. Areas were outlined manually and measured using Inage J (University of Wisconsin, Madison, WI, USA). The average area of leakage for each animal was used for group comparison using one-way ANOVA.

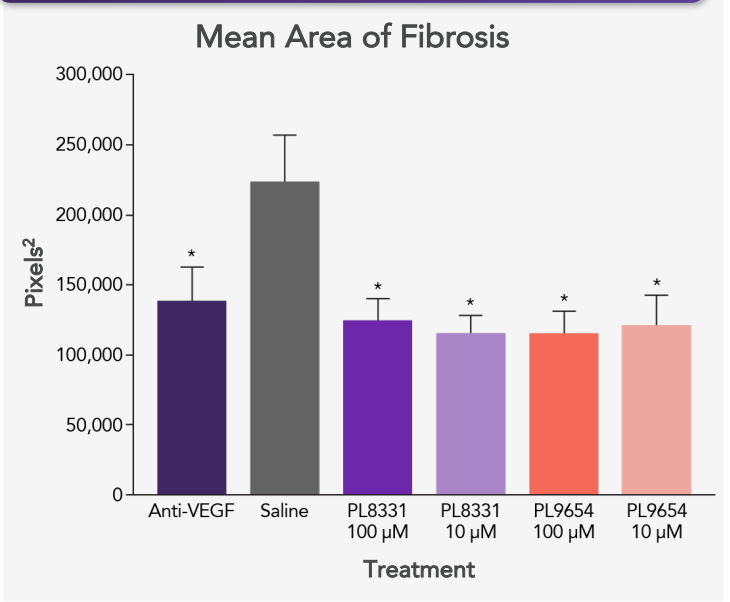
Figure 7. Mean Angiogenesis in Retinas of Mice Who Received Ocular Laser Burns



VEGF, vascular endothelial growth factor.

*$P \leq 0.05$. Angiogenesis was determined by immunohistochemistry using isolectin B4 staining. Mean areas of staining were used for group comparison using one-way ANOVA.

Figure 8. Mean Area of Fibrosis in Retinas of Mice Who Received Ocular Laser Burns



VEGF, vascular endothelial growth factor.

*$P \leq 0.05$. Fibrosis was determined by immunohistochemistry using positive collagen I staining. Mean areas of staining were compared using one-way ANOVA.

Summary

PL8177

Oral route of administration, high potency, no systemic exposure, extreme selectivity, and excellent preclinical efficacy result in a product profile of a very safe oral treatment for Ulcerative Colitis Clinical Proof of Principle studies initiate 2H2021

PL9643

Topical administration, high potency, no systemic exposure, excellent pre-clinical efficacy, rapid onset of action and no tolerability issues in Dry Eye clinical study result in a product profile of a very safe, tolerable and efficacious topical treatment for Dry Eye Disease Phase 3 studies scheduled for 2H2021

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Dry Eye Disease

May 21, 2021

Eric Donnenfeld, MD

What Is Dry Eye Disease?

- Dry eye is extremely common and is often underdiagnosed[1]
- Dry eye can negatively impact vision quality and can cause blurred vision, fluctuating vision, reduced contrast sensitivity, and increased glare[2-4]
- Quality of life and daily activities can be greatly impacted by dry eye symptoms[5]
- Significant psychological impact – patients have reported a willingness to trade years at the end of life to be free of dry eye disease (DED)[5]

1. Perry HD, Donnenfeld ED. Dry eye diagnosis and management in 2004. *Curr Opin Ophthalmol.* 2004;15:299-304. **2.** Pflugfelder SC, Beuerman RW, Stern ME, eds. *Dry Eye and Ocular Surface Disorders.* New York, NY: Marcel Dekker, Inc. 2004. **3.** Rolando M, Lester M, Macri A, Calabria G. Low spatial-contrast sensitivity in dry eyes. *Cornea.* 1998;17:376-379. **4.** Milijanovic B, Dana R, Sullivan DA, Schaumberg DA. Impact of dry eye symptoms on vision-related quality of life. *Am J Ophthalmol.* 2007;143:409-415. **5.** Schiffman RM, Walt JG, Jacobsen F, et al. Utility assessment among patients with dry eye disease. *Ophthalmology* 2003; 110:1412–1419.

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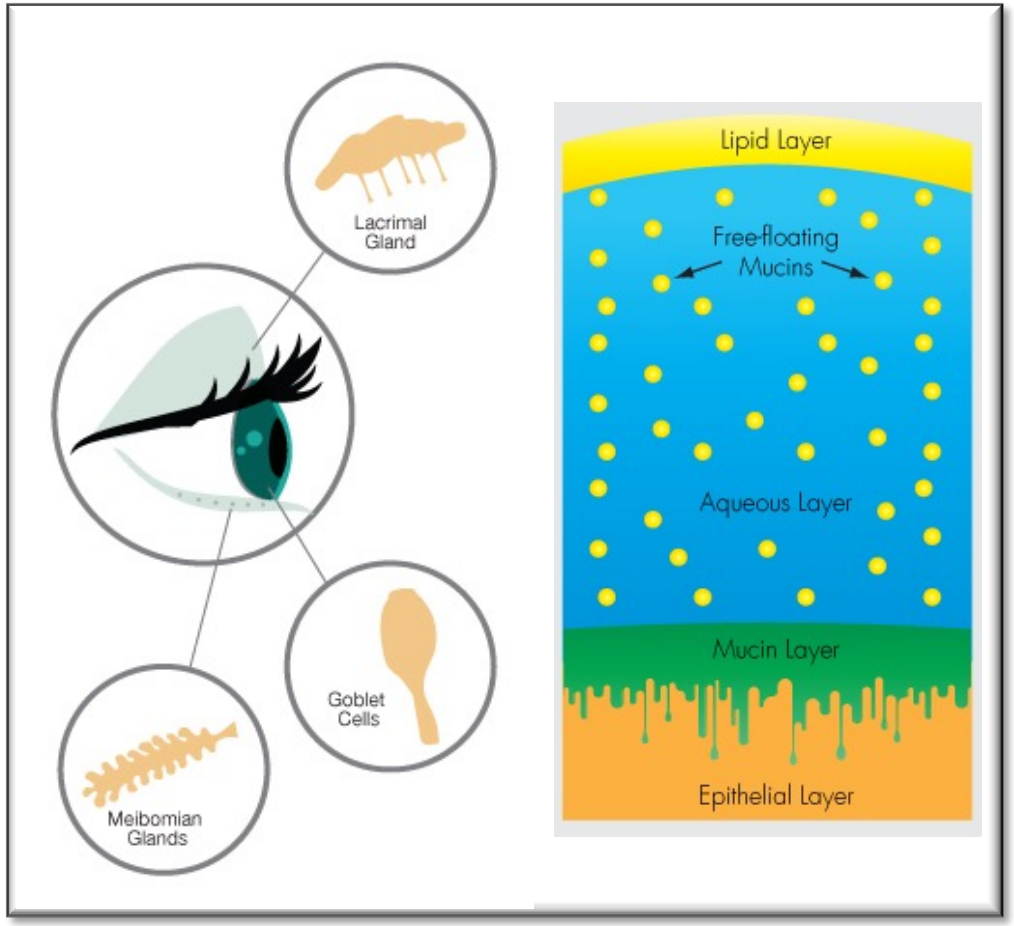
Background

- Dry eye disease
  - Multifactorial inflammatory and aqueous tear deficient disorder affecting the cornea and conjunctiva[1,2]
  - Characterized by ocular irritation and potential visual impairment[1,2]
- Existing dry eye therapies are often regarded as inadequate by many physicians and patients due to poor response, adverse effects (AEs), poor ocular tolerability, and prolonged interval preceding therapeutic activity[3,4]



1. DEWS Definition and Classification. The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop (2007). *Ocul Surf.* 2007;5(2):75-92. **2.** Bron AJ, et al. TFOS DEWS II pathophysiology report. *Ocul Surf.* 2017;15(3):438-510. **3.** Mah F, et al. PERSIST: Physician's Evaluation of Restasis® Satisfaction in Second Trial of topical cyclosporine ophthalmic emulsion 0.05% for dry eye: a retrospective review. *Clin Ophthalmol.* 2012;6:1971-1976. **4.** Tauber J, et al. Lifitegrast Ophthalmic Solution 5.0% versus Placebo for Treatment of Dry Eye Disease: Results of the Randomized Phase III OPUS-2 Study. *Ophthalmology.* 2015;122(12):2423-2431.

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Prevalence of Dry Eye Disease

Salisbury Study	Melbourne Study	Beaver Dam Study	WHS Study
14.4%	**5.5%**	**14.4%**	**6.7%**

However, the percentage of individuals who experience signs and symptoms of dry eye at one time or another due to environmental factors is 100%.

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DED Is One of the Most Common Eye Diseases in the United States[1]

AMERICAN ADULTS
suffer from symptoms of DED[2,3,a]

= 1 out of every 7 American Adults[2,3,a]

a Aged 25 to 84 years.

1. Schaumberg DA et al. *Am J Ophthalmol*. 2003;136(2):318-326. **2.** Paulsen AJ et al. *Am J Ophthalmol*. 2014;157(4):799-806. **3.** US Census Bureau. Annual estimates of the resident population for selected age groups by sex for the United States, states, counties, and Puerto Rico Commonwealth and municipios: April 1, 2010 to July 1, 2012. http://factfinder.census.gov. Published June 2013. Accessed September 15, 2015.

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DED Deserves Increased Attention

Symptoms of DED are among the most common complaints[1]

- 30% of patients who seek treatment from an ophthalmologist and 40% from an optometrist have symptoms consistent with DED[2]

DED may impair patients' ability to perform daily activities

- DED has been shown to:
  - Reduce work productivity[3,4]
  - Impair the ability to drive, watch television, use technology, and function socially[4,5]
  - Decrease reading speed[6,7]

DED is chronic and may be progressive[8]

- DED may progress to corneal damage; some loss of vision is possible[9]

1. Stern ME et al. *Int Rev Immunol.* 2013;32(1):19-41. **2.** Lemp MA. *Am J Ophthalmol.* 2008;146(3):350-356. **3.** Patel VD et al. *Curr Med Res Opin.* 2011;27(5):1041-1048. **4.** Yamada M et al. *Clinicoecon Outcomes Res.* 2012;4:307-312. **5.** Miljanović B et al. *Am J Ophthalmol.* 2007;143(3):409-415. **6.** Ridder WH III et al. *Optom Vis Sci.* 2013;90(1):37-44. **7.** Ousler GW III et al. *Cornea.* 2015;34(8):917-921. **8.** Ngo W et al. *Cornea.* 2013;32(9):1204-1210. **9.** National Eye Institute. Facts about dry eye. https://nei.nih.gov/health/dryeye/dryeye. Accessed June 25, 2015.

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A Phase 2, Multi-center, Randomized, Double-Masked, Placebo-Controlled Study Evaluating the Efficacy and Safety of PL9643 Ophthalmic Solution Compared to Placebo in Subjects with Dry Eye

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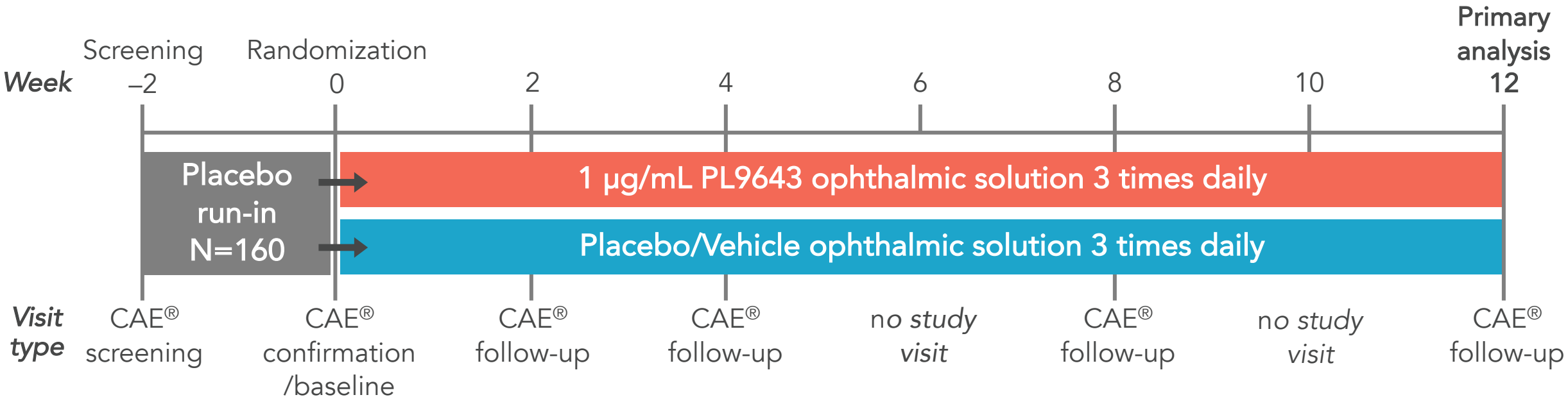
Study Design

12-week Phase 2, multicenter, 1:1 randomized, double-masked, placebo-controlled study



Study Subjects

- Adults with mild, moderate, or severe dry eye disease

Coprimary endpoints (Week 12)

- Inferior corneal fluorescein staining (sign)
- Ocular discomfort (symptom)

Secondary endpoints (Week 2 and Week 12)

Signs

- Fluorescein staining
- Lissamine green staining
- Tear film break-up time
- Conjunctival Redness

Symptoms

- Burning
- Dryness
- Eye discomfort
- Eye dryness
- Foreign body sensation
- Grittiness
- Itching
- Ocular discomfort
- Stinging

This phase 2 study evaluated the efficacy and tolerability of PL9643 in adults with dry eye disease

CAE®, controlled adverse environment.

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Co-Primary Endpoints & Patient Population

- Co-primary endpoints measured as change from baseline to Week 12:
  - Sign: Inferior corneal fluorescein staining
  - Symptom: Ocular discomfort

- Overall intent-to-treat (ITT) population (N = 160)
  - Patients with mild, moderate, or severe dry eye disease
  - No statistically significant differences in these Phase II endpoints, however, **PL9643 had a positive effect on many of the same endpoints that are being carried forward into the Phase III program**

- Moderate-to-Severe Population (N=54)
  - Duration of disease ≥ 5 years
  - ICS > 1
  - Eye discomfort ≥ 25 (1-100 scale)

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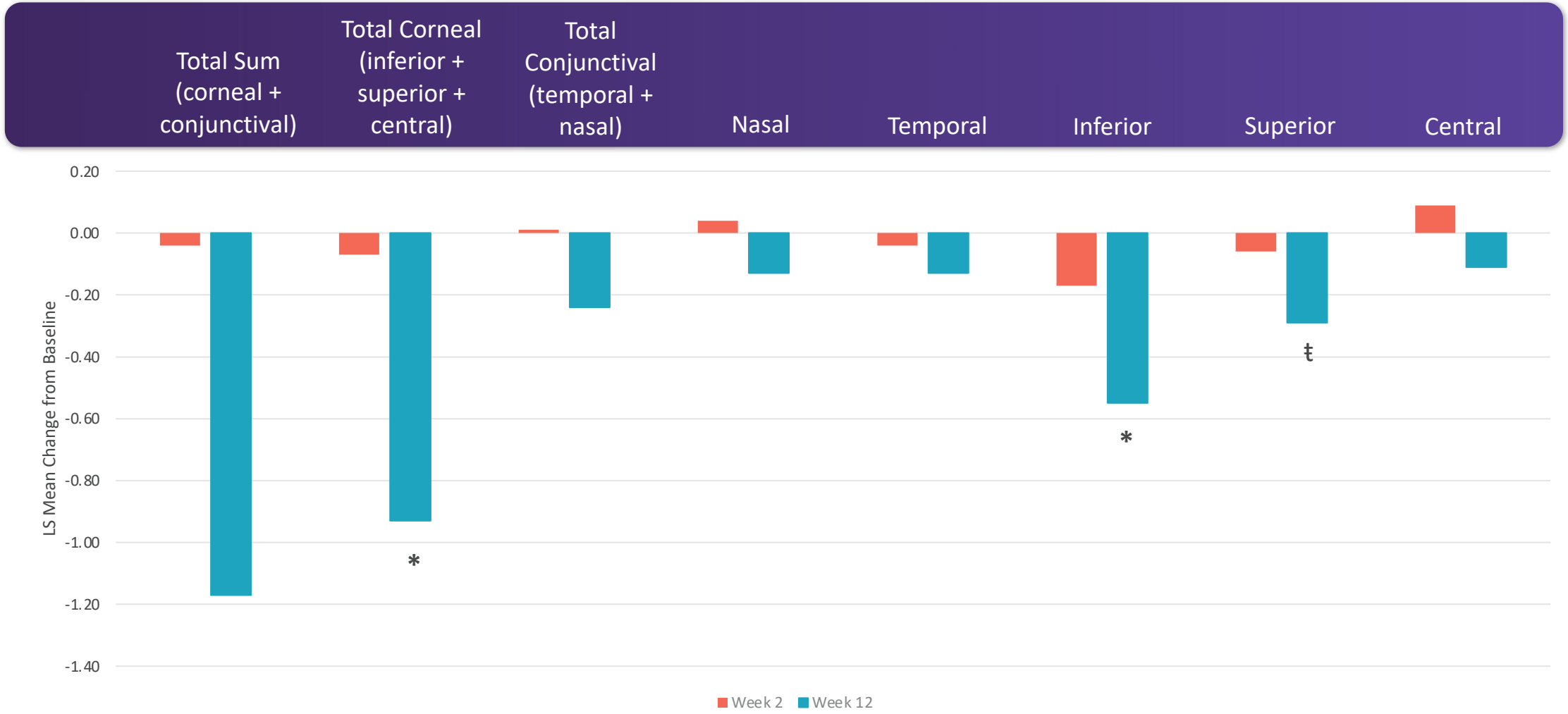
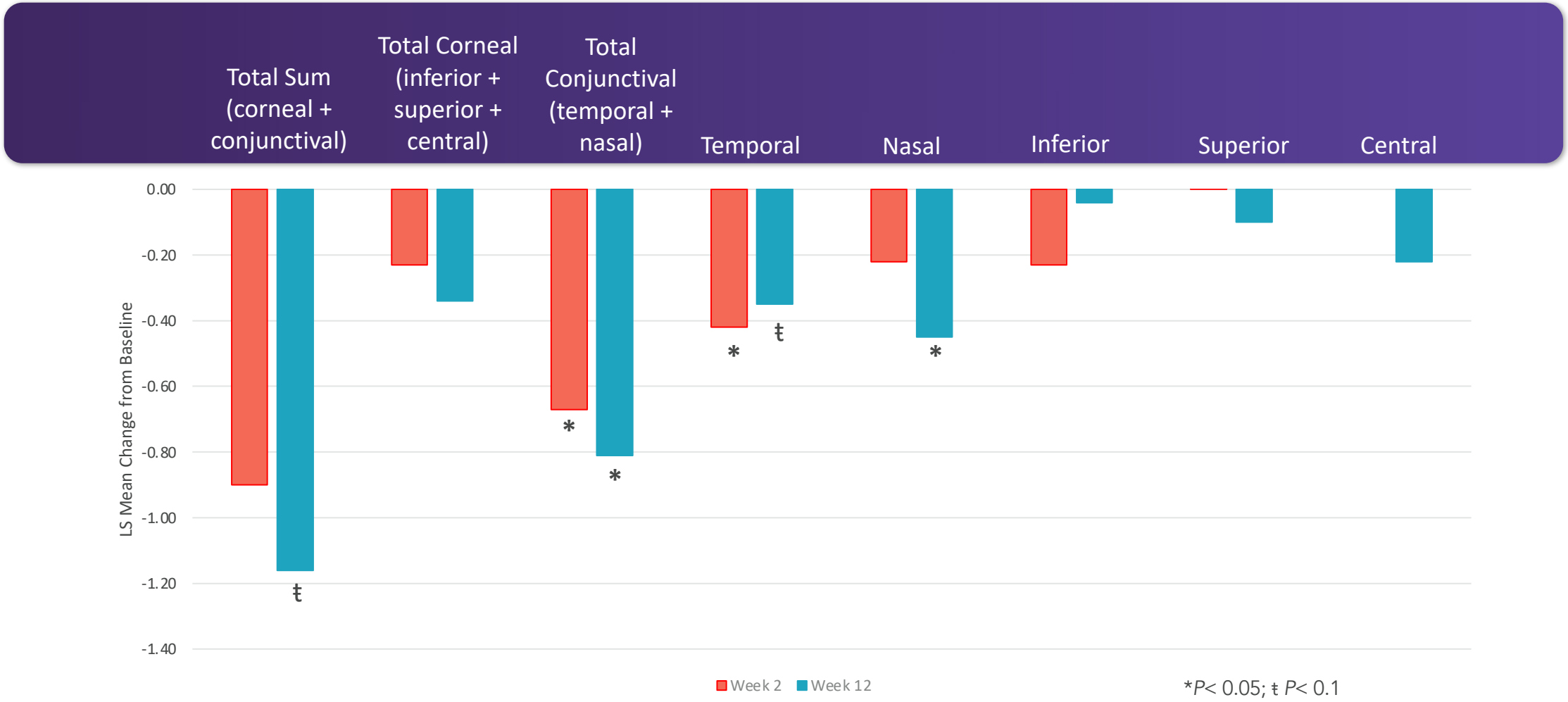
Differences between PL9643 and placebo (least squares mean change from baseline) in fluorescein staining in the Moderate-to-Severe Subgroup – observed data only



*$P<0.05$; ŧ $P<0.1$

Differences between PL9643 and placebo (least squares mean change from baseline) in Lissamine™ green staining in the Moderate-to-Severe Subgroup – observed data only



Population B included subjects with inferior corneal fluorescein staining > 1 at both Visits 1 (Week -1/Day -14) and 2 (Week 1/Day 1) Pre-CAE®, Eye Discomfort from Visual Analog Scale ≥ 25 at both Visits 1 (Week -1/Day -14) and 2 (Week 1/Day 1), Pre-CAE®, and a history of dry eye disease ≥ 5 years from time of enrollment.

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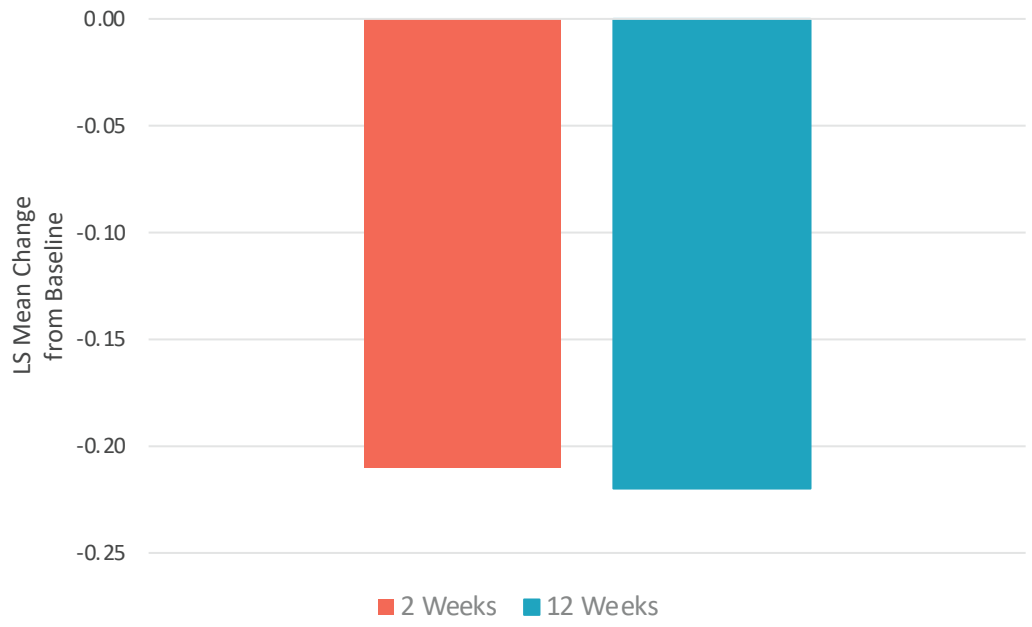
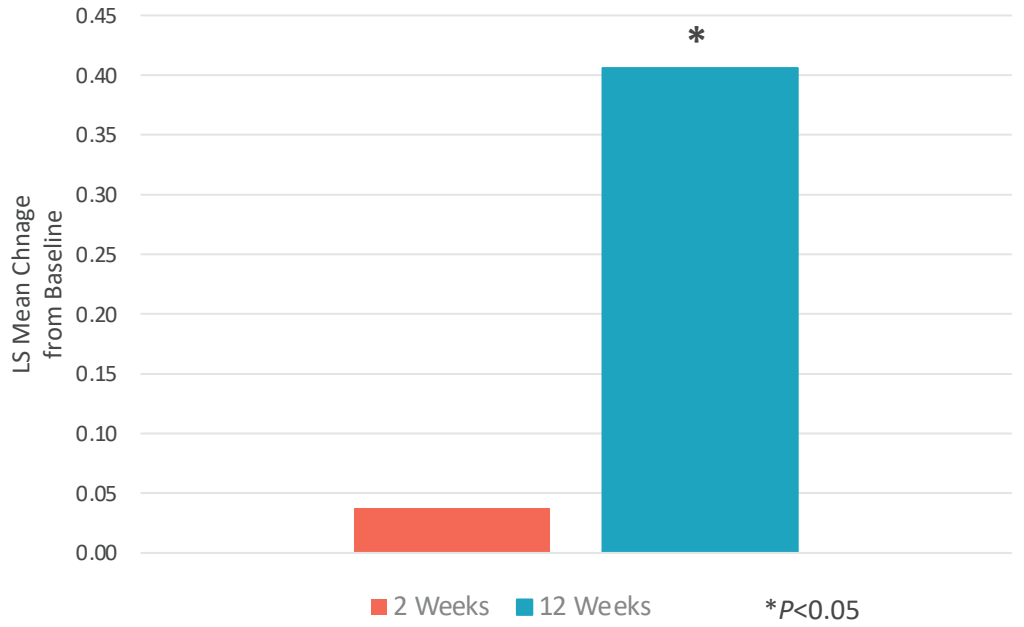
Differences between PL9643 and placebo (least squares mean change from baseline) in conjunctival redness and tear film break-up time in the Moderate-to-Severe Subgroup – observed data only

Conjunctival Redness



Tear Film Break-up Time



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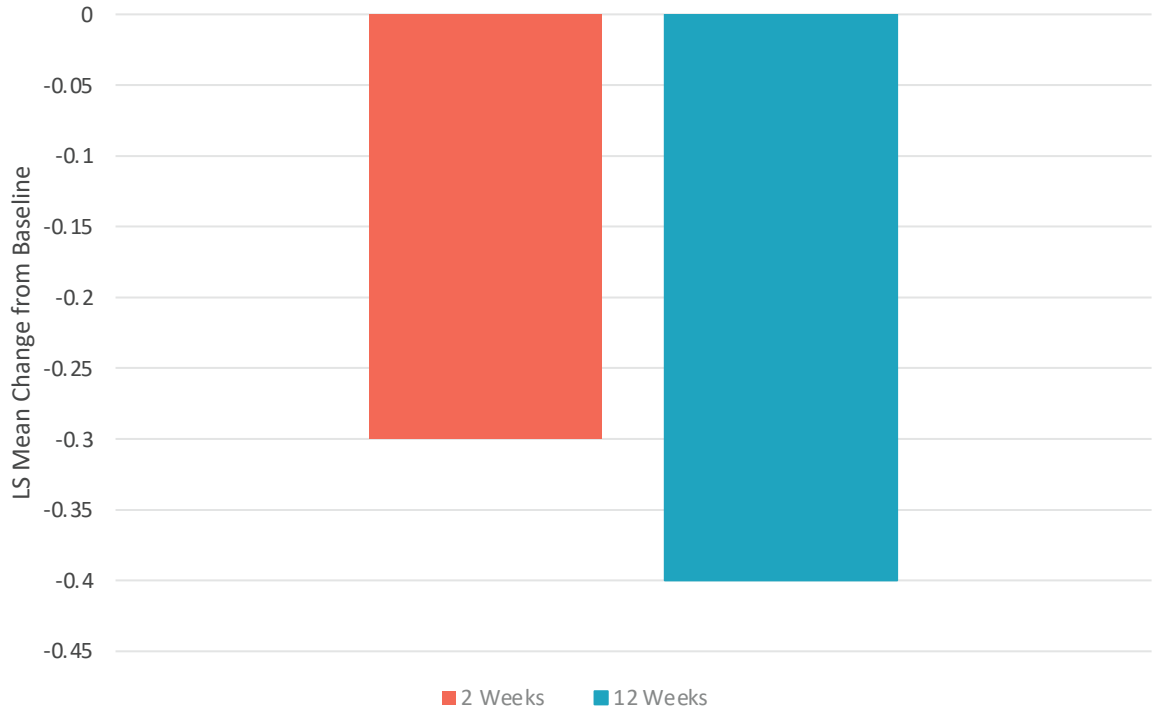
Co-Primary Endpoint (Single Question Scale): Differences between PL9643 and placebo (least squares mean change from baseline) in Ora Calibra® Ocular Discomfort Scale* scores in the Moderate-to-Severe Subgroup – observed data only

Ora Calibra® Ocular Discomfort Scale



For ocular discomfort, PL9643 demonstrated numeric improvement over vehicle as shown by negative change from baseline

*Measured on 0-4 scale.

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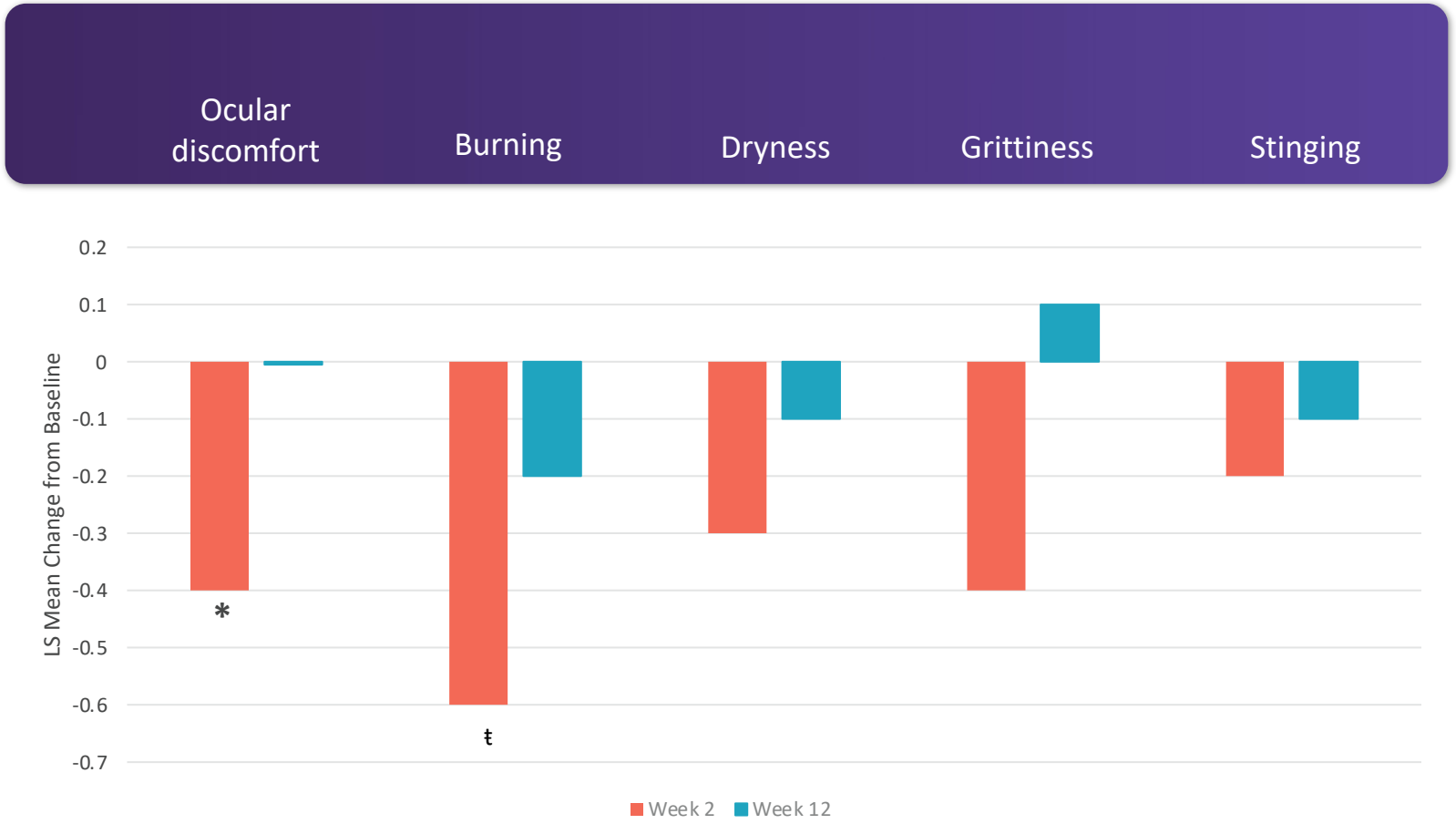
Secondary Endpoint (5-Question Scale): Differences between PL9643 and placebo (least squares mean change from baseline) in the Ora Calibra® Ocular Discomfort and 4-Symptom Questionnaire† scores in the Moderate-to-Severe Subgroup subgroup – observed data only



PL9643 demonstrated significant improvement in ocular discomfort over placebo at Week 2 (as shown by negative change from baseline)

*$P<0.05$; ŧ $P<0.1$

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Differences between PL9643 and placebo (least squares mean change from baseline) in components of the visual analog scale* in the Moderate-to-Severe Subgroup – observed data only

After 2 weeks, and also at 12 weeks, PL9643 demonstrated improvement over vehicle (as shown by negative change from baseline) in ocular symptoms

*VAS was measured on 0-100 continuous scale.

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Table 1. AEs by severity and relation to treatment

Event	Mild	Moderate	Severe	Total
PL9643	**13**	**3**	**0**	**16**
Non-ocular	12	3	0	15
Not related	10	3	0	13
Possibly related	1	0	0	1
Unlikely related	1	0	0	1
Ocular	1	0	0	1
Not related	1	0	0	1
Placebo	**17**	**4**	**2**	**23**
Non-ocular	9	4	2	15
Not related	9	3	2	14
Possibly related	0	1	0	1
Ocular	8	0	0	8
Not related	4	0	0	4
Possibly related	1	0	0	1
Probably related	1	0	0	1
Definitely related	2	0	0	2
Total	**30**	**7**	**2**	**39**

Safety

- No treatment-related serious AEs or ocular AEs were observed, and no subjects receiving PL9643 reported pain upon instillation of drops
- Fewer AEs occurred among subjects receiving PL9643 compared with placebo/vehicle

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Conclusions

- In subjects with moderate or severe dry eye disease, PL9643 ophthalmic solution led to benefits in signs and symptoms by the first evaluation at 2 weeks, which were maintained for the 12-week study duration
- PL9643 was well tolerated, with no treatment-related ocular AEs and a safety profile comparable to placebo/vehicle
- These positive results across multiple signs and symptoms support the continued development of PL9643 as a novel therapeutic option for treating dry eye disease

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A Novel Approach to Dry Eye Disease

- The melanocortin pathway provides a novel way to treat inflammatory conditions like dry eye disease by activating endogenous melanocortin receptors
- The efficacy of PL9643 as demonstrated in the phase 2 clinical trial presented here shows promise for treating both patient signs and symptoms in patients with DED
- This novel approach with the melanocortin agonist PL9643 may add to the options available to clinicians for treating DED

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The Advantages for Patients

- PL9643 is potent when compared to other treatments (eg, Restasis®); therefore, a smaller concentration was effective in treating DED signs and symptoms
- Patients experienced no stinging or ocular discomfort due to these drops, potentially leading to improved patient compliance
- Overall, a superior safety profile was observed with absence of any treatment-emergent adverse event
- PL9643 may provide a new option for those patients in whom other treatments failed or provided little to no relief

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THANK YOU

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PL9643-301 (MELODY-1) Study Overview: Efficacy and Safety of the Melanocortin Agonist PL9643 in Subjects With Moderate and Severe Dry Eye Disease

May 21, 2021

Study Design

- Multicenter, randomized, vehicle-controlled, double-masked, adaptive design Ph 3 study
- Evaluate the efficacy and safety of PL9643 in up to 320 adults with moderate or severe dry eye disease defined as:
  - Disease duration ≥ 5 years prior to screening
  - Inferior corneal staining score >1 at both Visit 1 (Day -14) and Visit 2 (Day 1)
  - Eye Discomfort score ≥ 25 as measured by the Visual Analog Scale (VAS) at both Visit 1 (Day -14) and Visit 2 (Day 1)
- All subjects will receive vehicle solution during a 2-week run-in period and then randomized 1:1 to receive either vehicle or PL9643 topical ophthalmic solution bilaterally 3 times daily for 12 weeks
- All subjects will be exposed to the Controlled Adverse Environment (CAE®) at each visit to assess suitability for study entry and sign and symptom endpoints
- Two interim assessments to be conduct on first 120 subjects (60 subjects/arm) at 2 weeks and 12 weeks
  - The **2 week interim assessment** will examine the conditional power ascribed to the primary clinical symptom and the 3 key secondary endpoints.
  - The **12 week interim assessment** will examine the conditional power ascribed to the primary clinical sign endpoints.
  - Depending on the results of either interim assessment, the sample size may be increased up to a maximum of 320 total patients, or enrollment into the study may remain at 240 total patients.

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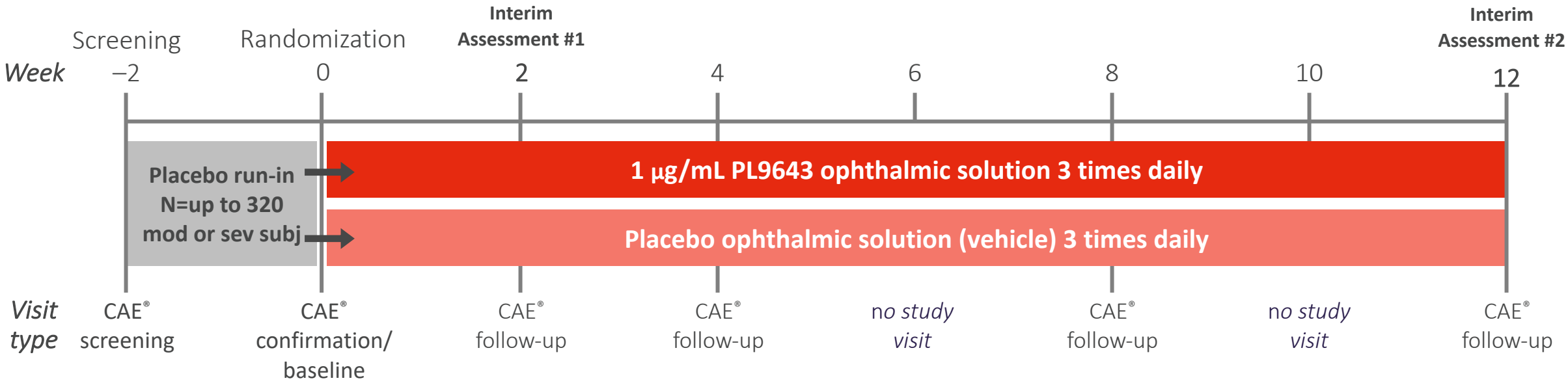
Study Design and Primary Endpoints: *12-week Phase 3, multicenter, 1:1 randomized, double-masked, vehicle-controlled adaptive design study*



Co-Primary Sign Endpts (Week 12)	Co-primary Symptom Endpt (Week 2)	Key Secondary endpoints (Week 2)
1) Inferior corneal fluorescein staining 2) Total Conjunctival lissamine green staining (Nasal + Temporal Regions)	3) Ocular discomfort	*Signs* 1) Total Conjunctival Lissamine green staining (Nasal + Temporal Regions) *Symptoms* 2) Burning 3) Eye discomfort

CAE®, controlled adverse environment

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Additional Endpoints

Secondary Endpoints: Signs

- Temporal lissamine green staining
- Conjunctival redness
- Nasal lissamine green staining
- Tear film break-up time (TFBUT)
- Corneal sum fluorescein staining
- Total sum lissamine green staining
- Total sum fluorescein staining
- Superior corneal fluorescein staining

Secondary Endpoints: Symptoms

- Grittiness (Ocular Discomfort & 4-Symptom Questionnaire)
- Ocular Discomfort Scale
- Foreign Body Sensation (VAS)
- Pain (VAS)
- Itching (VAS)
- Eye Dryness (VAS)

- **Tertiary Endpoints**
  - Variables not listed as co-primary, key secondary, or secondary endpoints will be evaluated as tertiary endpoints per the statistical analysis plan.

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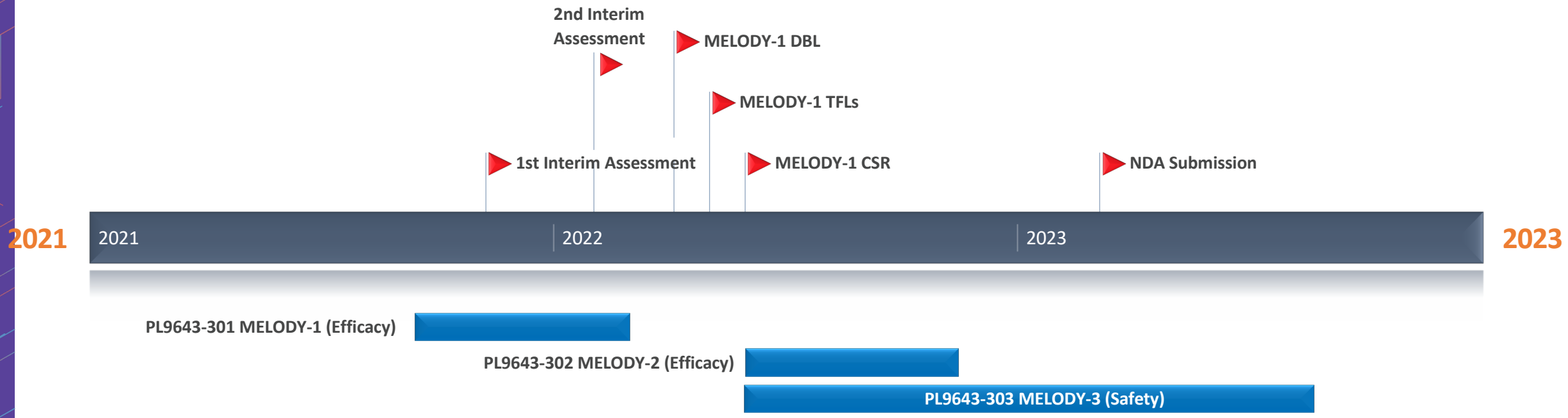
PL9643 DED Program Timelines



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Retinopathy Preclinical Data and Clinical Opportunity

Investor Day
May 21, 2021

Preclinical Proof-of-Concept

To validate melanocortin receptors as therapeutic targets for retinal vascular diseases, Palatin's melanocortin agonist compounds were tested in two relevant animal models

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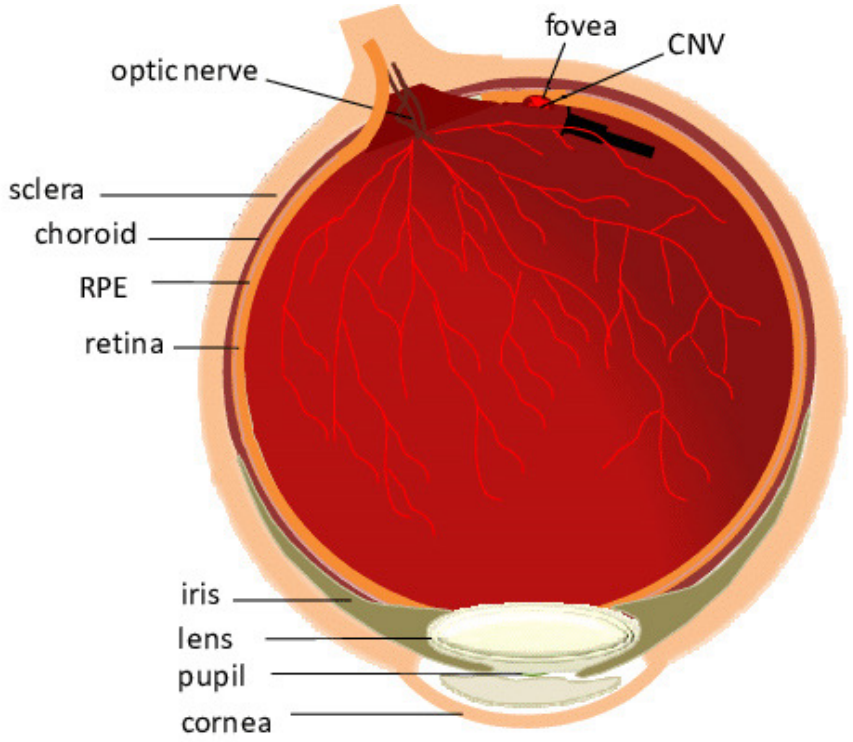
Laser-Induced Choroid Neovascularization (CNV) Model



This mouse model recapitulates the main features of the exudative form of human age-related macular degeneration (AMD)

Palatin compounds demonstrated that engaging the melanocortin receptors led to improved outcomes, including:

- Decreased CNV leakage grades and area
- Reduced neovascularization
- Reduced collagen deposition

1. Nowak-Sliwinska P. Anti-angiogenic treatment for exudative age-related macular degeneration: New strategies are underway. *Curr Angiogenes.* 2012;1:318-334.

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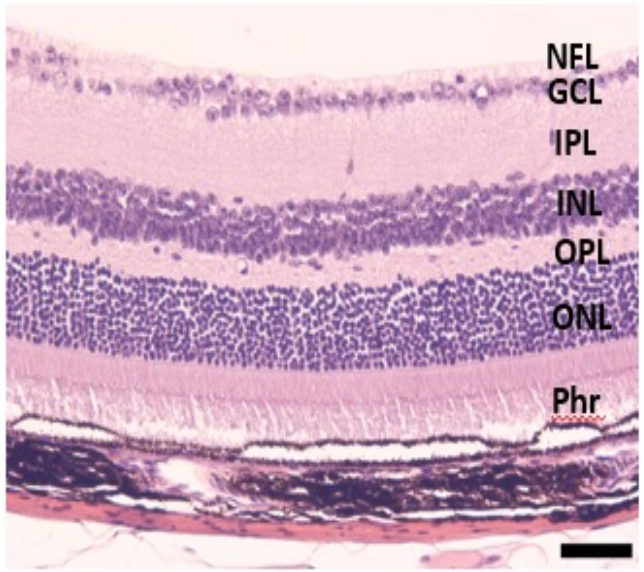
Diabetic Retinopathy Model

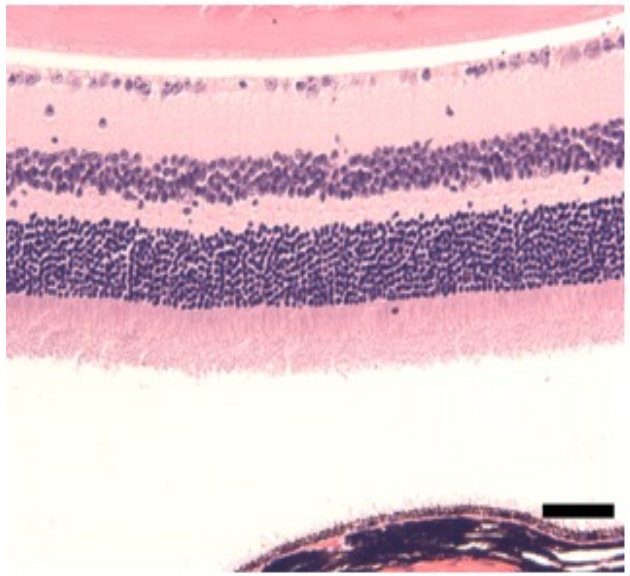
Melanocortin agonist demonstrated key indicators of improve retinal health, including:

- Preserved retinal anatomy
- Suppressed pro-inflammatory cytokine to healthy control levels
- Increased levels of IL-10, a marker of inflammation resolution

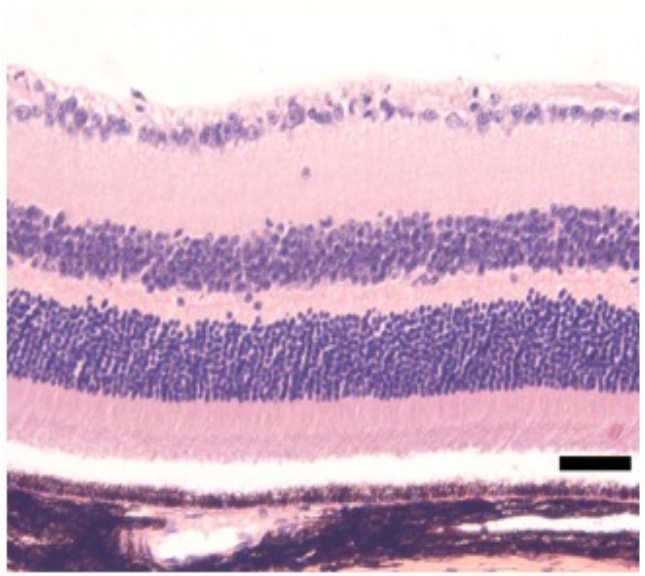
Healthy Control



Diabetic Untreated



Diabetic melanocortin agonist



This rodent model develops diabetic retinopathy like that seen in humans

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Therapeutic Candidate Selection

Criteria for lead clinical candidate:

- High potency at melanocortin receptors 1 and 5
- Demonstrated efficacy in preclinical animal models
- Enabling pharmacokinetics
- Desirable solubility profile
- Straight-forward synthesis path
- Excellent IP position

PL9654 was chosen based on the above criteria

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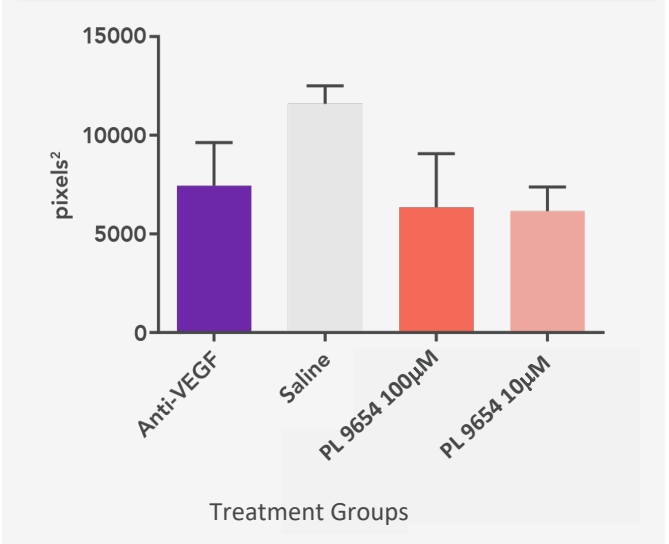
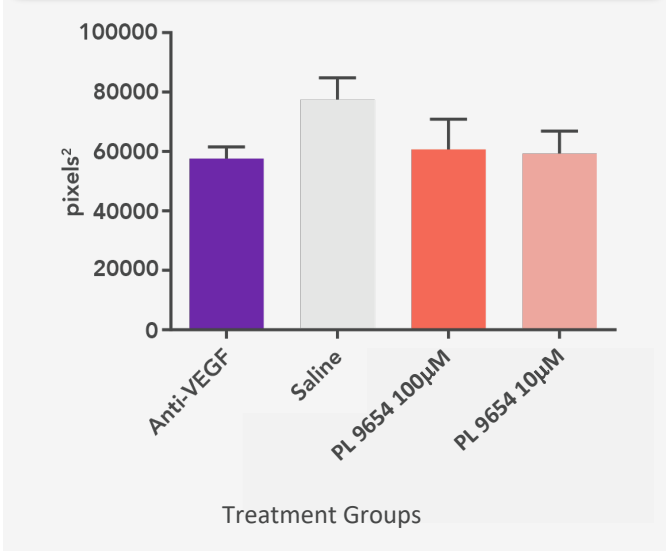
PL9654 in a Mouse CNV Model

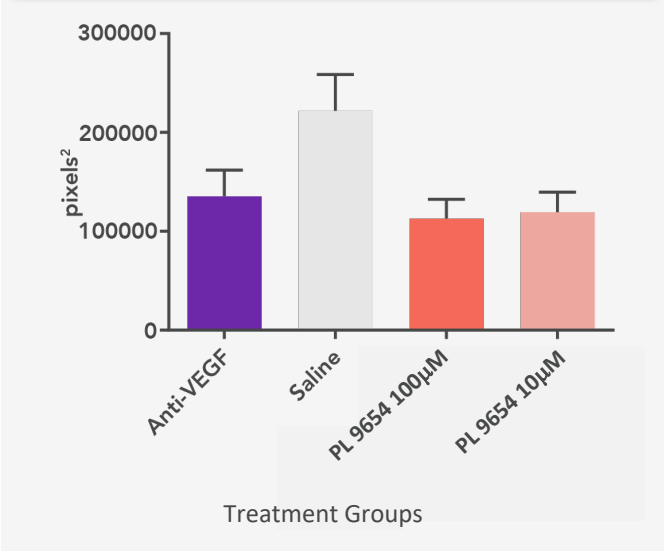
MEAN LEAKAGE AREA



MEAN AREA OF ANGIOGENESIS



MEAN AREA OF FIBROSIS



- PL9654 showed therapeutic activity comparable to an anti-VEGF control
  - CNV leakage area reduced compared to controls
  - Angiogenesis area reduced compared to controls
  - Fibrosis area reduced, trending better than anti-VEGF

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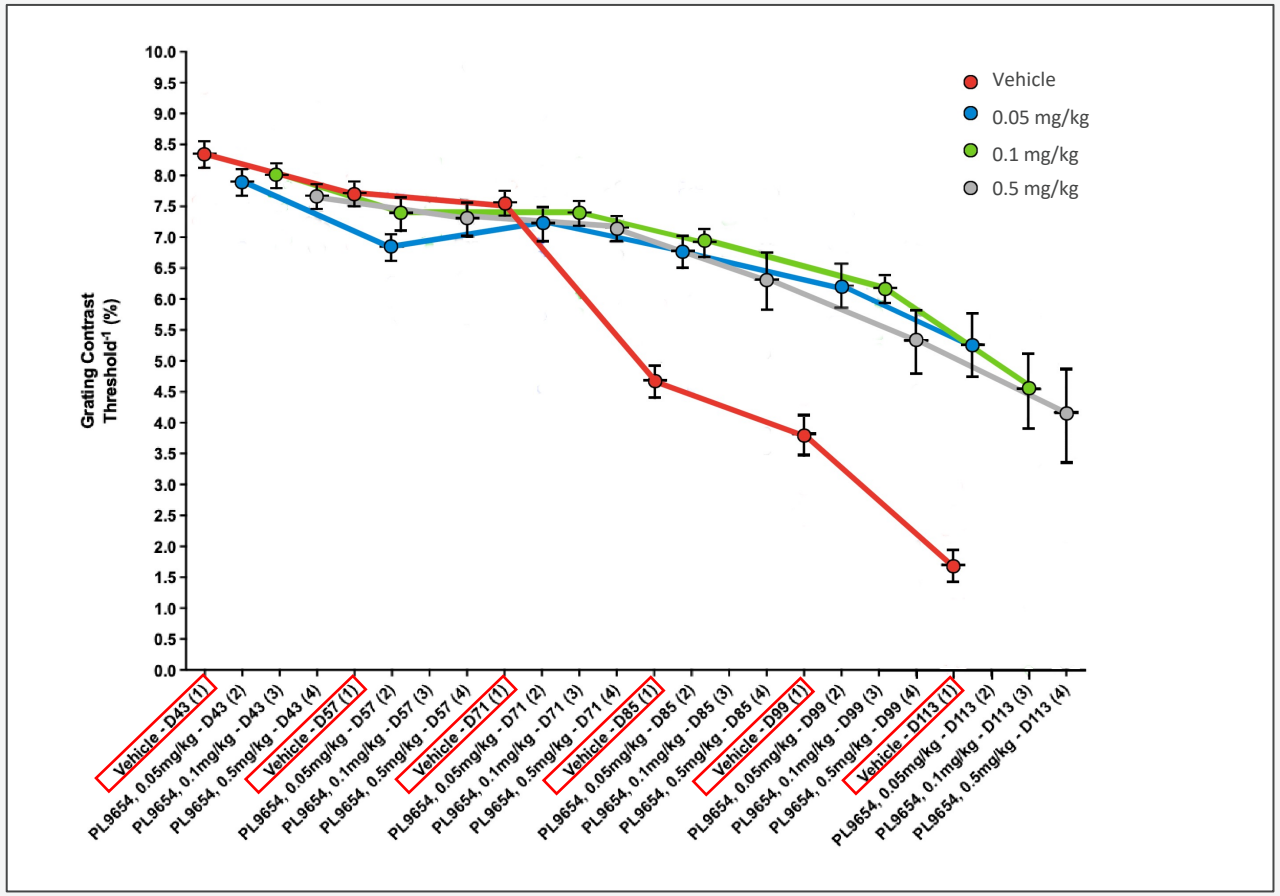
PL9654 in a Rat Diabetic In-Life Retinopathy Model

CONTRAST VISION



PL9654 preserves contrast vision as compared to controls

A second measure of visual acuity demonstrated similar efficacy to this measurement

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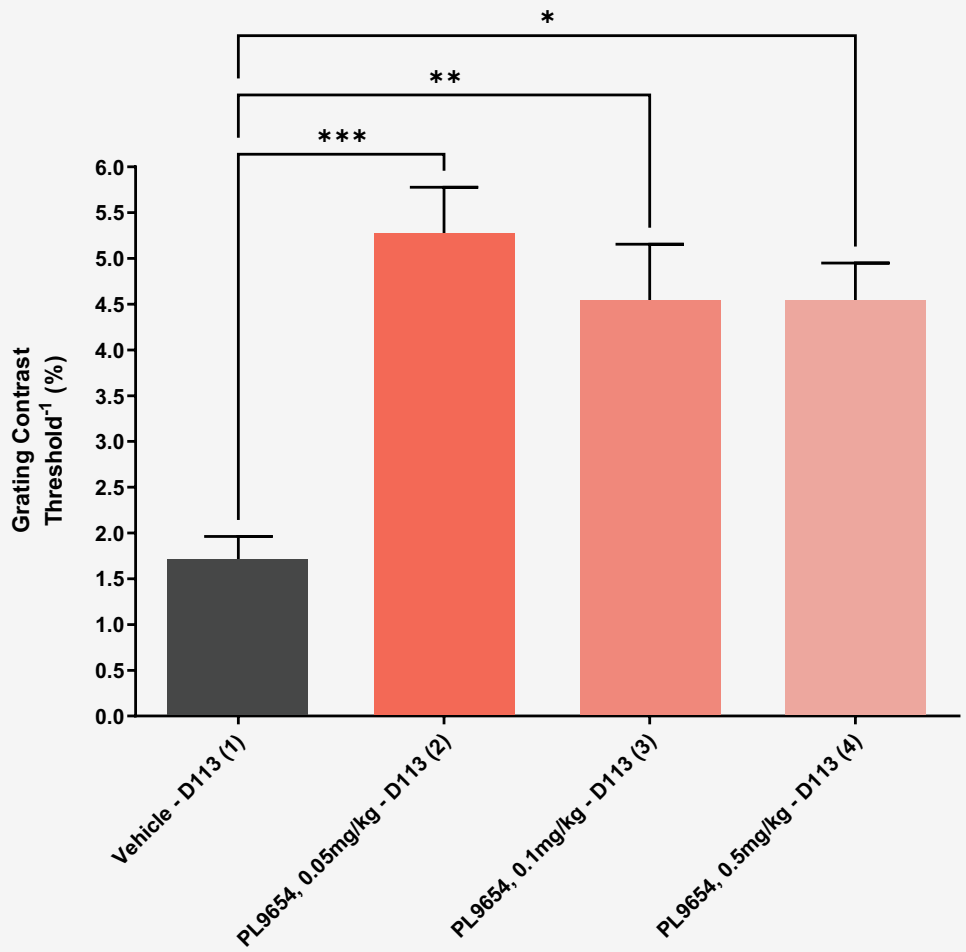
PL9654 Preserves Contrast Sensitivity in a Rat Diabetic Retinopathy Model

Final Mean Change in Contrast Sensitivity

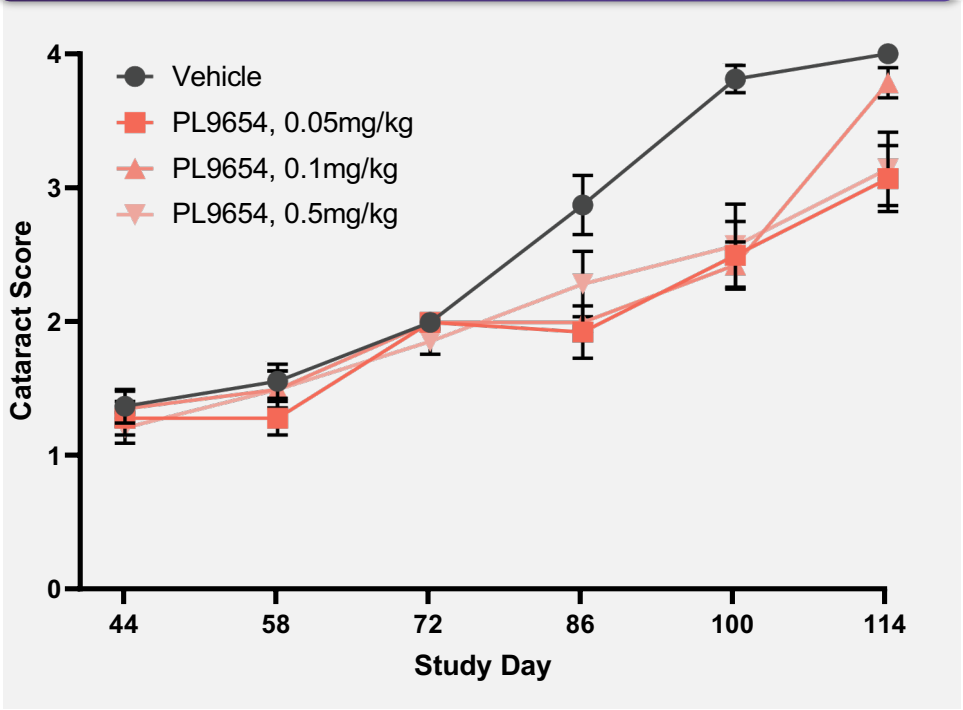


This prevention of visual function loss demonstrates the potential utility of melanocortins in retinal vascular diseases

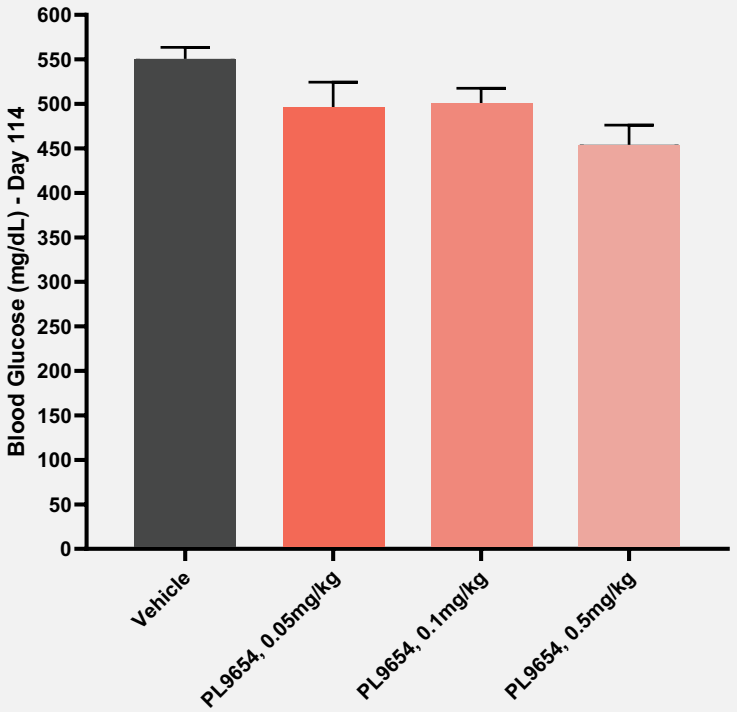
*P<0.02; **P<0.004; ***P<0.0002

PL9654 Delays Cataract Formation and Doesn't Affect Blood Glucose Levels in Rat Diabetic Retinopathy In-Life model

CATARACT SCORE



BLOOD GLUCOSE LEVELS



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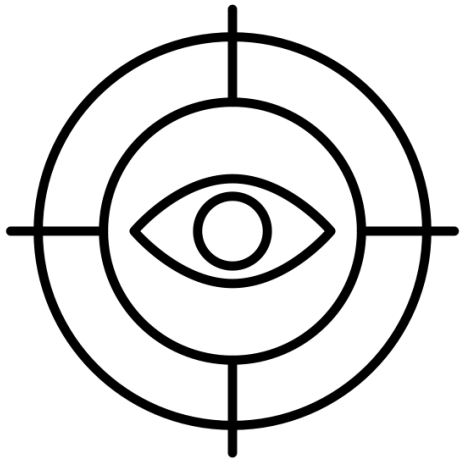
PL9654 Is Progressing as a Retinopathy Therapeutic Candidate



Ongoing Activities

- Additional preclinical models and measurements
- Genomic and proteomic characterization of treated animal models
- Extensive PK
- Toxicology studies

Determine optimal Route of Administration to maximize value to patient

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