## OPHTHALMIC THERAPEUTICS UPDATE

JESSICA STEEN OD, FAAO, DIPL ABO

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## JESSICA STEEN OD FINANCIAL DISCLOSURES

- Speakers Bureau-Carl Zeiss Meditec, Bausch and Lomb, Viatris, Thea Pharma, Alcon, Allergan, Astellas, Dompé
- Consultant-Bausch and Lomb, Balance Ophthalmics, Carl Zeiss Meditec, Opus Genetics, Viatris, Allergan, Astellas, Alcon, Radius XR, iCare, Glaukos, Eyenovia, Tarsus, Orasis, Topcon, Envision Health Technologies, LKC, Astra Zeneca, Lifecyte Innovations
- Shareholder-Clearside Biomedical, Annexon Bio (<0.01% ownership)
- *All relevant relationships have been mitigated*

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## *Making an Impact*

**Filling an unmet need**

***Common conditions***

***Rare disease***

**Providing additional options**

**Novel products**

**Repurposed molecules**

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## *Framework for Development*

**PDUFA (1992)**

Authorized the FDA to collect fees from drug companies-important role in expediting drug approval process

*Is there industry influence when 45% of the FDA's budget is funded through user fees?*

For 2026: Application fee: $4,682,003 + program fee ($442,213)
Either 10 months; or 6 months if granted priority review

When the FDA takes too long or too little time to review a drug→criticism
Balance between regulation and efficiency

***Remember, the FDA doesn't guarantee safety of a product***

*It ensures that the data presented is credible and ensures benefit with acceptable risks*

***Balance of safety and efficacy***

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## *How do you stay up to date?*

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## HOW DO YOU STAY UP TO DATE?

Medscape OPHTHALMOLOGY MedPulse

TOP STORIES

Semaglutide Linked to Cause of Vision Loss

36-Hour Window Safe for Globe Injury Repair

Can We Limit Arbovirus Transmission During the Olympics?

NEWS

Cataracts

Uveitis in Children Linked to Higher Cataract Risk

Retinal Issues Rise After Cataract Surgery

Diabetes

Thyroid Warning on GLP-1s Could Raise Overdiagnosis Risk

**Evewire News**

09.11.2026

**Bausch + Lomb Receives CE Mark Approval for SeeLyra Femtosecond Laser**

*Eyewire News*

09.11.2026

**Ziemer to Showcase Femtosecond, Refractive Surgery Innovations at ESCRS 2026**

*Eyewire News*

09.10.2026

**Zeiss Launches AT Lucia Toric 721P at ESCRS 2026**

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## Break Down

*Agents that may raise IOP*

*IOP lowering agents*

*Front → back of the eye*

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## NEW OCULAR STEROIDS

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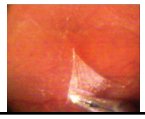
## NOT-NEW: INJECTABLE STEROIDS

- Triamcinolone acetonide
  - Kenalog (periocular—sub-Tenon's or subconjunctival)
    - Off-label for intraocular injection
  - Triesence-preservative-free Kenalog
    - Used for intravitreal injection



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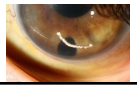
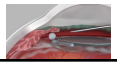
## INJECTABLE STEROIDS

- Intravitreal implants-provide sustained release of steroid
  - Ozurdex (dexamethasone 0.7mg) 3-6 months
  - Retisert (fluocinolone acetonide 0.59mg)
  - Iluvien (fluocinolone 0.19mg)—off-label for posterior uveitis-up to 3 years!
  - Yutiq (fluocinolone 0.18mg)—indicated for treatment of non-infectious posterior uveitis-3 years
- Dexamethasone **intraocular** suspension 9% (Dexycu)
  - 5uL dose at the conclusion of cataract surgery



Dexycu


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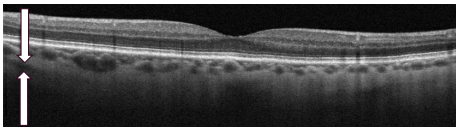
## Retinal Disease

*Alternative routes of drug delivery*

*Suprachoroidal space*

J code received June 21, 2022

***Triamcinolone acetonide injectable suspension 40mg/ml (Xipere)***



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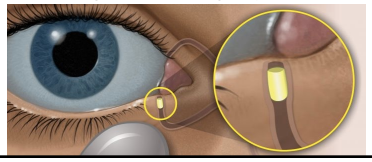
## STEROID INSERT

- Dextenza (dexamethasone insert 0.4mg)
  - Intracanalicular insert approved November 2018
  - Indicated for the treatment of ocular pain and inflammation following ocular surgery and treatment of ocular itching associated with allergic conjunctivitis



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## OTHER "NEW" STEROIDS

- Loteprednol etabonate suspension 1% (**Inveltys**)
  - Proprietary mucus penetrating particle technology to increase drug delivery
  - BID for post surgical dosing
- Loteprednol etabonate suspension 0.25% (**Eysuvis**)
  - Approved October 27, 2020
  - Short-term (up to two weeks) for the signs and symptoms of dry eye disease. QID
    - Ocular discomfort severity scale 0-100 (improvement from about 70-58 after 2 weeks). Improved about 9 points with vehicle
    - Improvement in conjunctival hyperemia (CCLRU scale)

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## LOTEMAX SM

- Loteprednol etabonate ophthalmic gel 0.38%
- SubMicron Technology
  - Greater anterior chamber penetration
  - Faster drug dissolution
  - *On label dosing: three times daily vs. four times daily for loteprednol 0.5%*

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## CLOBETASOL

- Clobetasol propionate ophthalmic suspension 0.05% (Byqlovi)
  - *"Active Pharmaceutical Nanoparticle Technology"-no shaking required*
  - Approved for the treatment of post-operative inflammation and pain following ocular surgery BID x 2 weeks
  - Synthetic corticosteroid, preserved with BAK (0.0036%), 1% IOP elevation in clinical trials
- Available as a topical (non-ophthalmic) ointment-considered to be a strong steroid

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## IOP LOWERING AGENTS

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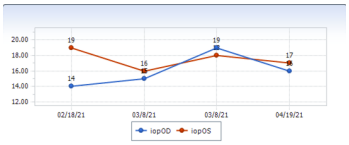
## 56 YEAR OLD AFRICAN AMERICAN FEMALE

- 56 year old African American female referred for evaluation due to suspicion of glaucoma secondary to optic disc appearance
  - No family history of glaucoma
  - No systemic diagnoses; no systemic medications

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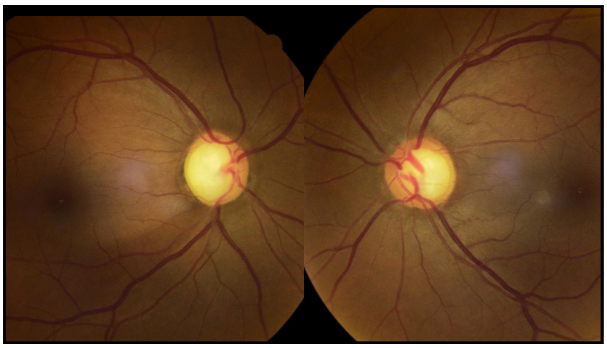

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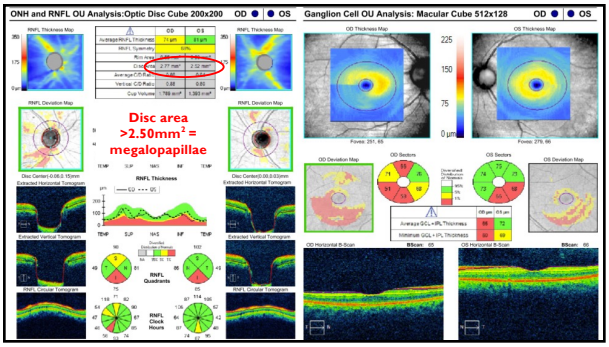


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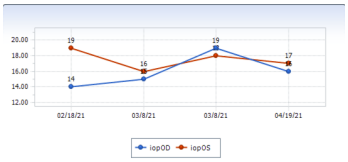
## MANAGEMENT

- 1) Medication(s)?
  - Topical & oral
- 2) Laser?
- 3) Surgical options?

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## IOP LOWERING MEDICATION OPTIONS

- First line treatment:
  - Prostaglandin analog
    - Best adherence at FDA approved dosing
- What does 'maximum medical therapy' mean?
  - ***Classically***:
    - 1) Prostaglandin analog
    - 2-4) CAI
      - Alpha-2 agonist
      - Beta blocker
    - Rho kinase inhibitor
    - ?Pilocarpine

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## "NEW" PROSTAGLANDINS

- Latanoprostene bunod 0.024% (Vyzulta)
  - Latanoprost acid + butanediol mononitrate
    - Butanediol monohydrate releases NO which increases outflow through the trabecular meshwork and Schlemm's canal
      - Relaxes trabecular beams
- Latanoprost 0.005% preservative free (Iyuzeh)
- Bimatoprost 0.01% preservative-free gel (Zolymbus)

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Preservative-Free Bimatoprost 0.01% Ophthalmic Gel for Glaucoma Therapy: A Phase III Randomized Controlled Trial

*Francisco J. Muñoz-Negrete, MD, PhD,*†† Fotis Topouzis, MD, PhD,‡ Francesco Oddone, MD, PhD,§ Sylvie Nissle,|| Dariusz Rokicki, MD,|| Ingrida Januleviciene, MD, PhD,¶ Paul Harasymowycz, MD,#** and Ingeborg Stalmans, MD, PhD†‡‡‡*

***PF-bimatoprost 0.01% vs. BAK-preserved bimatoprost 0.01%***

***Noninferiority at 12 weeks***

***Lower incidence of corneal staining in PFB group (33.2% vs. 42.3%); baseline 33.9% and 35.3%***

***Less aggravation of conjunctival hyperemia 18.3% vs. 30.4% at 12 weeks; baseline 44.5% and 43.4%***

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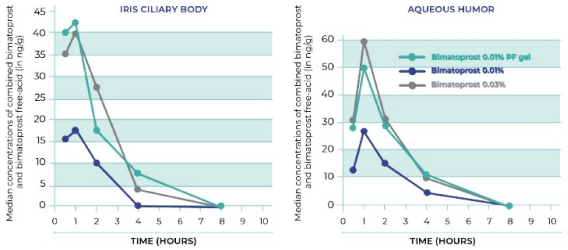


**Bimatoprost 0.01% PF gel and bimatoprost acid concentration in ICB and AH after instillation in rabbits' eyes**

Erb C, Topouzis F, Jayaram H, Allan F, Nisslé S, Muñoz-Negrete FJ, Stalmans I. Preclinical and Clinical Pharmacokinetics of a New Preservative-Free Bimatoprost 0.01% Ophthalmic Gel to Treat Glaucoma and Ocular Hypertension. J Ocul Pharmacol Ther. 2025 Jan-Feb;41(1):8-16.

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## RHO KINASE

- Rho kinase family includes proteins which regulate cell shape, motility, proliferation, and apoptosis
  - **Regulate smooth muscle contraction in the trabecular meshwork and ciliary body**
- *May also affect ocular blood blow and retinal ganglion cell survival*
  - *Role in cardiovascular procedures, corneal procedures*
  - *Role in development of fibrosis*

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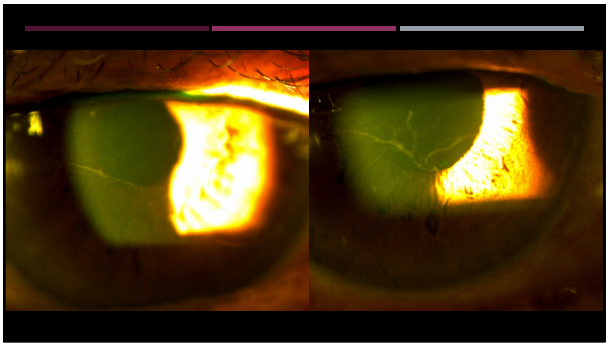
## RHO KINASE INHIBITOR/NOREPINEPHRINE TRANSPORT INHIBITOR

- **Increase trabecular outflow**
- **Lower episcleral venous pressure**
- Netarsudil 0.02% (Rhopressa)
  - QHS
- Netarsudil/latanoprost 0.02%/0.005% (Rocklatan)
  - QHS
- Hyperemia-most common effect
  - Typically improves over time
  - *When do you see your patients back after altering medical therapy?*
- Subconjunctival hemorrhage
- Less common-corneal verticillata
  - Level of the epithelium

65



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## WHERE DO RHOPRESSA & ROCKLATAN FIT IN?

- Efficacy is similar to timolol 0.5% (BID)
  - **In clinical trials
- Ideally a second line treatment
  - Seems to work better with low/moderate IOP (<25mmHg)
- Advantage of once daily dosing vs. other typical second line medication
- Cost?

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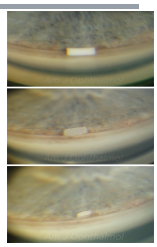
## *Sustained release*

***Bimatoprost implant 10mcg***



Sustained release bimatoprost
Equivalent to about 2-3 drops of bimatoprost 0.01%
Drug release complete in 3-4 months

197 eyes, 94.9% pseudophakic, 41.6% prior SLT, mean age 80.4
Effect approximately 1 year; reduction in medication use
16.9% underwent SLT within first 12 months

*No corneal edema related to implant observed*

Teymoorian S, Craven ER, Nguyen L, Werts E. Real-World Study of the Effectiveness and Safety of Intracameral Bimatoprost Implant in a Clinical Setting in the United States. Clin Ophthalmol. 2024 Jan 19;18:187-199.

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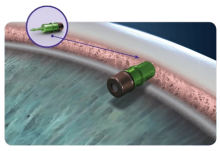
## *Sustained release*

***Travoprost titanium implant***
FDA approved December 14, 2023
Not refillable



36 month data: 70% (fast-release) and **68% (slow-release)** fewer or same medications as baseline

Mean IOP reduction: 8.3mmHg (fast-release) and 8.5mmHg (slow-release)

Berdahl JP, Sarkisian SR Jr, Ang RE, Doan LV, Kothe AC, Usner DW, Katz LJ, Navratil T; Travoprost Intraocular Implant Study Group. Efficacy and Safety of the Travoprost Intraocular Implant in Reducing Topical IOP-Lowering Medication Burden in Patients with Open-Angle Glaucoma or Ocular Hypertension. Drugs. 2024 Jan;84(1):83-97.

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ANTERIOR SEGMENT MEDICATIONS

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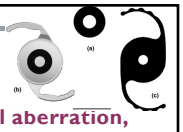
## Presbyopia



**Small aperture = reduced spherical aberration, increased depth of focus**

***Pilocarpine 1.25% ophthalmic solution (Vuity)***
FDA approved October 30, 2021; now on label for twice daily dosing (March 2023)

***Pilocarpine 0.4% ophthalmic solution (Qlosi)***
FDA approved October 18, 2023; preservative-free, up to twice daily dosing

*Currently under investigation:*
***Phentolamine 0.75% + pilocarpine 0.4%***
***Pilocarpine 0.302% + phenylephrine 0.624% + pheniramine 0.0772%***

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## Presbyopia

***1.75% aceclidine (Vizz)***
***Small molecule muscarinic Ach receptor agonist***

***71% 3+ lines improvement at 30 minutes***
***40% 3+ lines at 10 hours! (two drops)***

PDUFA date August 8, 2025

FDA approved July 31, 2025

***Pooled data: 20.1% instillation site irritation, 13.2% visual impairment (dimness), 9% hyperemia***

***CLARITY1, 2, 3***

85

## Presbyopia

***Carbachol 2.75%/0.1% brimonidine (Yuvezzi)***
***Fixed dose combination-demonstrated superiority over individual components***

***30 minutes through 10 hours-1 drop***

FDA approved January 29, 2026

***Headache, blurred vision; hyperemia 2.8% (vs. 10.7% with carbachol alone)***

***BRIO I, BRIO II***

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## Reversal of Mydriasis

***Preservative-free phentolamine 0.75% (Ryzumvi)***

***Nonselective alpha 1 and 2 blocker***

***FDA approved for the treatment of pharmacologically-induced mydriasis (3+ years of age)!!***

FDA Approved September 27, 2023

***MIRA-1, 2, 3, 4***

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## Myopia

***SYD-101 0.01% atropine; preserved with BAK***

***STAR-primary endpoint met(!); 4 years, 800 kids 3-14***

***"the data do not support the effectiveness"***

CRL received October 23, 2025

***Available in the EU and UK***

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## Anterior Segment

FDA approved October 18, 2021

***Dry Eye Disease***

**Varenicline solution nasal spray 0.03mg**

*Activates the trigeminal parasympathetic pathway = increased production of basal tear film*

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## TYRVAYA (VARENICLINE SOLUTION NASAL SPRAY 0.03MG)

- One spray in each nostril twice daily
- Most common adverse reaction:
  - **Sneezing** (82%) of patients
  - *Cough, throat irritation, nose irritation*

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## Anterior Segment

***Tryptyr (acoltremon 0.003%) ophthalmic solution- signs and symptoms of dry eye disease***

***Transient receptor potential melastatin 8 (TRPM8) agonist → accesses the efferent pathway to stimulate the lacrimal functional unit***

***COMET-1, COMET-2***

FDA Approved May 29, 2025

***Single dose vials, 50% instillation site pain, <1% dropout due to ocular adverse event***

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## Anterior Segment

***Dry eye disease associated with meibomian gland dysfunction***

***Miebo (NOV03 100% perfluorohexyloctane [$F_6H_8$])***

FDA Approved May 18, 2023

***Prevents evaporation and stabilizes the tear film***

***SEECASE, GOBI, MOJAVE, KALAHARI***

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## Anterior Segment

***Vevye (CyclASol 0.1% cyclosporine A in EyeSol)***

***EyeSol = water-free technology that increases surface contact time***

***ESSENCE1 & ESSENCE2***

FDA Approved June 8, 2023

***Twice daily dosing; multidose; smaller drop size***

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## Anterior Segment

***Demodex blepharitis***

***Xdemvy (Lotilaner ophthalmic solution 0.25%)***

***Demodex is more common than we think***

***Antiparasitic agent***

FDA Approved July 25, 2023

***Twice daily x 6 weeks (duration to match organism life cycle)***

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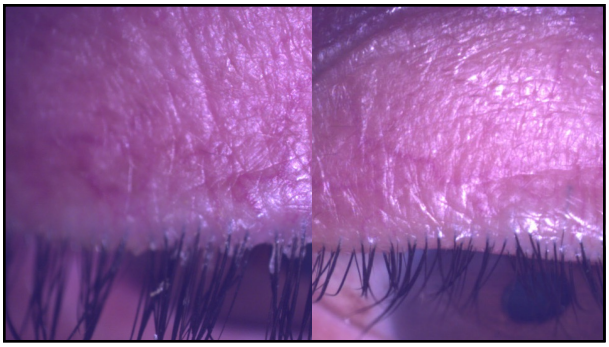

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## Anterior Segment

PDUFA Date November 23, 2023

CRL received November 27, 2023

New PDUFA Date April 12, 2025

CRL received April 3, 2025

New PDUFA Date December 16, 2025…extended to March 16, 2026…CRL.

***Dry eye disease, allergic conjunctivitis***

**Reproxalap**

***RASP modulator-reduces inflammation through reduction of cytokine release and inflammasome activity***

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## Anterior Segment

***AZR-MD-001 ophthalmic ointment 0.5%; (selenium sulfide)***

***Ophthalmic keratolytic***

***ASTRO phase 3-patients with MGD; completion November 2025***

***Twice weekly at bedtime***

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## Anterior Segment

***Neurotrophic keratitis***

***Oxervate (Cenegermin-bkbj ophthalmic solution) 0.002%***

***Recombinant human nerve growth factor***

***6x daily for 8 weeks***

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## Cenegermin

***Phase 3 clinical trial underway-intranasal cenegermin in NAION***

***Actively (or soon-to-be) recruiting-25 sites in the US, Australia, and UK***

***NAION (50-80) with symptoms within 14 days of planned first dose, vision 15-65 ETDRS letters (20/63-20/500)***

https://clinicaltrials.gov/study/NCT07453888

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## Acute optic neuritis

***Phase 3 clinical trial underway; activates SGK-2→IGF-1 & BDNF***

***First episode of optic neuritis (18-50) with symptoms within 12 days of first treatment***

***OCS-05 (Privosegtor) 3mg/kg/day IV for 5 treatment days + methylprednisolone vs. methylprednisolone alone***

***Current site: MI, SC, TX***

https://clinicaltrials.gov/study/NCT07623668

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## *Anterior Segment*

***Lacrifill canalicular gel***

***25g cannula***

***Crosslinked hyaluronic acid filler***

***Non-inferior to plugs; indicated for up to 6 months, irrigated with saline***

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## 70-YEAR-OLD BLACK MALE

- Presented for evaluation of suspicion of glaucoma and blurred vision in both eyes
  - Type 2 diabetes mellitus, managed with diet and "Amiclear"
- BCVA 20/40 OD 20/30 OS
- No APD
- IOP 16mmHg OD 14mmHg OS (CCT 534 µm OD 544 µm OS)
- Nuclear sclerosis OU, PVD OU

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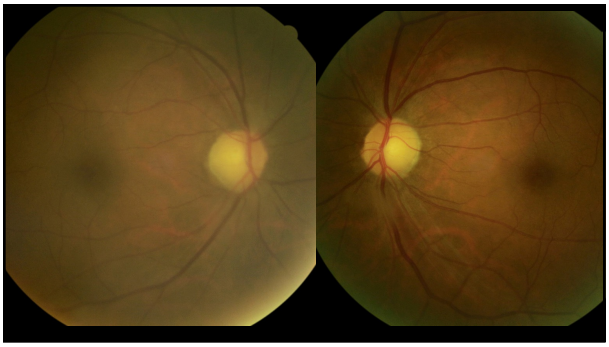

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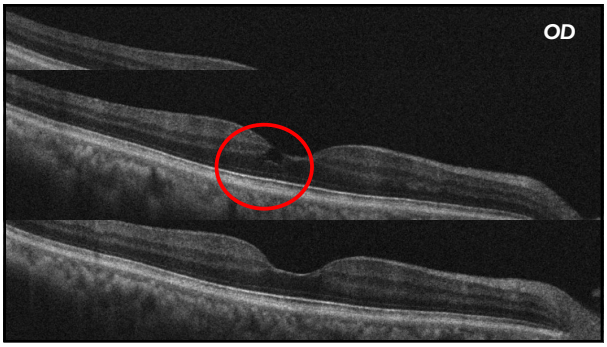


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## *Could this be early macular telangiectasia type 2?!*

***Neurodegenerative disease process affecting Muller cells***

***Muller cells maintain inner BRB***

***DM, obesity, hypertension, and cardiovascular disease are common***

***First stage: deep capillary involvement***

***Widening of the foveal pit → hyporeflective cavities → disruption of the ELM***

***Ciliary neurotrophic factor (CNTF) encapsulated cell therapy***

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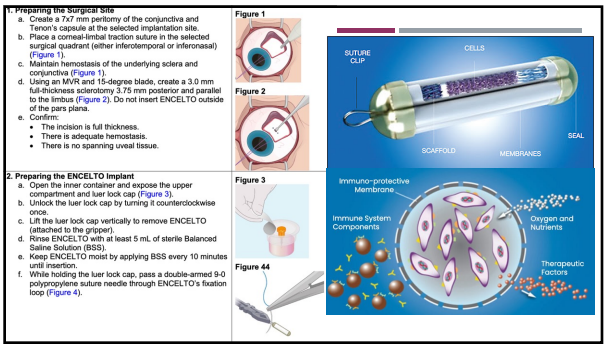


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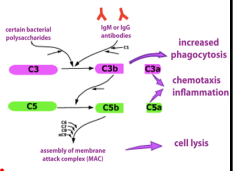
## Retinal Disease

### Dry age-related macular degeneration

*CFH polymorphism increases risk of AMD (complement control protein)*

*Components of drusen and oxidative stress can trigger complement cascade → apoptosis*




***Complement over-activation is implicated in pathogenesis of AMD***

*Classical, alternative, lectin pathways converge to activate C3 C5 activation can lead to increased VEGF expression by the RPE*

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## AREDS3 VITAMIN

- Incorporates "B vitamins"
  - Increase cell metabolism
  - Reduction of inflammation
- Gene expression profile data
  - In vitro data, seems to support synergistic effect of AREDS2 + B-vitamins
    - B5, B6, serum folate

Merle et al 2022. Nutrients

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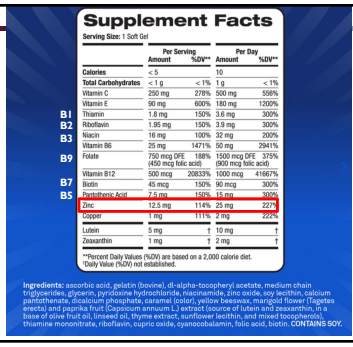

**Supplement Facts**

Serving Size: 1 Soft Gel

| | Per Serving Amount | %DV** | Per Day Amount | %DV** |
|---|---|---|---|---|
| Calories | < 5 | | 10 | |
| Total Carbohydrates | < 1 g | < 1% | 1 g | < 1% |
| Vitamin C | 250 mg | 278% | 500 mg | 556% |
| Vitamin E | 90 mg | 600% | 180 mg | 1200% |
| B1 Thiamin | 1.8 mg | 150% | 3.6 mg | 300% |
| B2 Riboflavin | 1.95 mg | 150% | 3.9 mg | 300% |
| B3 Niacin | 16 mg | 100% | 32 mg | 200% |
| Vitamin B6 | 25 mg | 1471% | 50 mg | 2941% |
| B9 Folate | 750 mcg DFE (450 mcg folic acid) | 188% | 1500 mcg DFE (900 mcg folic acid) | 375% |
| Vitamin B12 | 500 mcg | 20833% | 1000 mcg | 41667% |
| B7 Biotin | 45 mcg | 150% | 90 mcg | 300% |
| B5 Pantothenic Acid | 7.5 mg | 150% | 15 mg | 300% |
| Zinc | 12.5 mg | 114% | 25 mg | 227% |
| Copper | 1 mg | 111% | 2 mg | 222% |
| Lutein | 5 mg | † | 10 mg | † |
| Zeaxanthin | 1 mg | † | 2 mg | † |

**Percent Daily Values (%DV) are based on a 2,000 calorie diet.
†Daily Value (%DV) not established.

**Ingredients:** ascorbic acid, gelatin (bovine), dl-alpha-tocopheryl acetate, medium chain triglycerides, glycerin, pyridoxine hydrochloride, niacinamide, zinc oxide, soy lecithin, calcium pantothenate, dicalcium phosphate, caramel (color), yellow beeswax, marigold flower (Tagetes erecta) and paprika fruit (Capsicum annuum L.) extract (source of lutein and zeaxanthin, in a base of olive fruit oil, linseed oil, thyme extract, sunflower lecithin, and mixed tocopherols), thiamine mononitrate, riboflavin, cupric oxide, cyanocobalamin, folic acid, biotin. **CONTAINS SOY.**

*Vs. 80mg in AREDS2*

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## *Pegcetacoplan (Syfovre)*

*Blocks C3, C3b (and C5 downstream)-synthetic peptide*

*FILLY (Phase 2) slows GA rate of progression in a dose-dependent manner*

*DERBY & OAKS (Phase 3)*

*Endpoints met in OAKS. very close in DERBY*

*Pooled data met*

FDA Approved February 17, 2023

*43.5kDa;*

*$C_{1970}H_{3848}O_{947}S_4$*

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## *Pegcetacoplan (Syfovre)*

*Post-hoc analysis of GALE: 5-year data in non-subfoveal GA*

*EOM and EM dosing "saved" approximately 1.5 years vs "projected sham"*

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## *Avacincaptad Pegol (Izervay)*

**GATHER1 (Phase 2b/3)-endpoints met**
**GATHER2 (Phase 3)-primary endpoint met**

*Interesting: slowed iRORA to cRORA change—and drusen to iRORA*

*Safety signal: CNV rate 9.0% in GATHER1 and 6.7% in GATHER2*

*Expect that if an efficacy signal was identified at month 12, the difference between groups should continue to increase at months 18 and 24*

FDA Approved August 4, 2023

*3.5 year data from GATHER2 extension*

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## *Avacincaptad Pegol (Izervay)*

*3.5-year data from GATHER2 extension*

*Monthly dosing provides maximal benefit*

***EOM is nearly as effective for first 2-3 years***

*Sham for 2 years; then monthly ACP-smallest absolute benefit*

*Real-world injection interval was approximately every 6 weeks*

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## *ANX007 (vonaprument)*

**Investigational drug in GA; for preventing vision loss(!!)**

**ARCHER and ARCHER II**

*C1q inhibitor; intravitreal injection monthly*

***Neuroprotective effects?!***

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## PHOTOBIOMODULATION

- LIGHTSITE III
  - 100 subjects, 148 eyes; 24 month analysis; randomized PBM to sham 2:1
    - Active sham
  - High risk intermediate AMD
  - Improves cellular processes (cytochrome C oxidase in the mitochondria at the level of the electron transport chain)
- **Primary endpoint met!**
  - Difference between treatment and sham group at 13 months (& 2 years!)
    - 5.5 letters at month 13, 5.9 at month 24
    - PBM group: decrease in new onset GA

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## PHOTOBIOMODULATION

- FDA authorization November 4, 2024 of Valeda Light Delivery System
  - Less than 5 minutes per session, undilated
  - 9 sessions over 3-5 weeks; every 4 months over 24 months (LIGHTSITE III)
    - 590nm (yellow), 66nmm (red), and 850nm (NIR)
  - Impact on NO, VEGF, and electron transfer
- ***Challenges:***
  - ***Drop out: 14% in the treatment group, 23.5% sham; groups were imbalanced.***
  - ***Small sample size***
  - ***27 visits a year!!!!***
  - ***5.4 letter improvement in treatment group, 3 letters in sham—is this clinically significant?***
    - ***24 month data—sham decreased almost to baseline***
    - ***Improvement in BCVA as a primary endpoint is a major limitation-what about anatomy?!***

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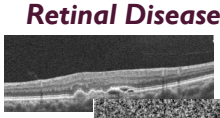
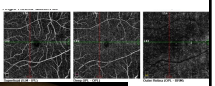
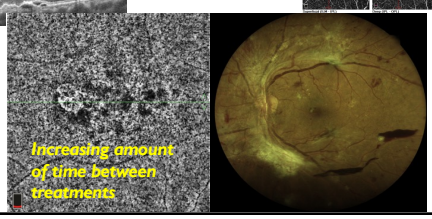
## *Retinal Disease*

***Durability***





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## *Retinal Disease*

**Neovascular AMD**
**(and diabetic eye disease…more generally, retinal vascular disease)**

**Extracellular VEGF pathways**
***VEGF-A***
***VEGF-B***
***VEGF-C***
***VEGF-D***
***PlGF***

**TKI pathways**

**TIE2 activation pathways**

**Integrin pathways**

**Gene therapy**

***Unmet needs in management of retinal disease?***

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## Eylea HD: High Dose Aflibercept (8mg)

***PHOTON (DME) and PULSAR (nAMD) & now FDA approved for macular edema after RVO (11/20/2025)***

***12 and 16 week dosing regimens vs. Eylea x q8weeks***

FDA Approval
August 18, 2023

***93% (PHOTON) and 83% (PULSAR) maintained q12 weeks or greater***

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**DOSAGE AND ADMINISTRATION**

- **Neovascular (Wet) Age-Related Macular Degeneration (nAMD)**
  - The recommended dose for EYLEA HD is 8 mg (0.07 mL of 114.3 mg/mL solution) administered by intravitreal injection every 4 weeks (approximately every 28 days +/- 7 days) for the first three doses, followed by 8 mg (0.07 mL of 114.3 mg/mL solution) via intravitreal injection once every 8 to 16 weeks, +/- 1 week. (2.2)
- **Diabetic Macular Edema (DME)**
  - The recommended dose for EYLEA HD is 8 mg (0.07 mL of 114.3 mg/mL solution) administered by intravitreal injection every 4 weeks (approximately every 28 days +/- 7 days) for the first three doses, followed by 8 mg (0.07 mL of 114.3 mg/mL solution) via intravitreal injection once every 8 to 16 weeks, +/- 1 week. (2.3)
- **Diabetic Retinopathy (DR)**
  - The recommended dose for EYLEA HD is 8 mg (0.07 mL of 114.3 mg/mL solution) administered by intravitreal injection every 4 weeks (approximately every 28 days +/- 7 days) for the first three doses, followed by 8 mg (0.07 mL of 114.3 mg/mL solution) via intravitreal injection once every 8 to 12 weeks, +/- 1 week (2.4)

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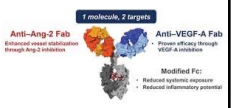
## FARICIMAB (VABYSMO)

*Permanent J-code as of October 1, 2022*

- FDA approved January 28, 2022-the newest! **(currently)
- Bispecific antibody (dual-pathway inhibiting)
  - Targets angiopoietin-2 (Ang-2) and VEGF-A
    - Ang-2 and VEGF work in concert-increases permeability and inflammation
- TENAYA and LUCERNE (nAMD)
  - Vs. aflibercept
  - Treated every 3-4 months (after 4 monthly doses)
    - 80% of individuals were able to go 3+ months between treatments in the first year
  - YOSEMITE and RHINE (DME)




*Reported 19% market share in AMD*

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## COST EFFECTIVENESS OF ANTI-VEGF

- $2625 aflibercept (8mg/0.07mL)-Eylea HD
- $2190 faricimab (6mg/0.05mL)-Vabysmo
- $1850 brolucizumab (6mg/0.05mL)-Beovu
- $1850 aflibercept (2.0mg/0.05mL)-Eylea
- $1170 ranibizumab (0.3mg/0.05mL)-Lucentis
- $70 bevacizumab (1.25mg/0.05mL)-Avastin

- **Bevacizumab is typically the first line anti-VEGF in the USA**

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formulation of bevacizumab under development to treat wet AMD. While the FDA acknowledged the NORSE TWO pivotal trial met its safety and efficacy endpoints, the Agency concluded it could not approve the BLA during this review cycle due to several CMC issues, open observations from pre-approval manufacturing inspections, and a lack of substantial evidence.

- Currently no authorization ophthalmic formulation of bevacizumab in the USA
  - Bevacizumab gamma authorized in EU and UK 2024 for nAMD
- NORSE 2-superiority trial
  - 113 patients received 12 bevacizumab-vikg (monthly)
  - 115 patients received 5 ranibizumab injections 1, 2, 3, 6, 9)-based on PIER (2008) dosing regiment from the package label
- ***Who did better?***

For Ophthalmic Intravitreal Injection Only (2.1)

**Neovascular (Wet) Age-Related Macular Degeneration (AMD) (2.2)**
LUCENTIS 0.5 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

Although not as effective, patients may be treated with 3 monthly doses followed by less frequent dosing with regular assessment. In the nine months after 3 initial monthly doses, less frequent dosing with 4-5 doses on average is expected to maintain visual acuity while monthly dosing may be expected to result in an additional average 1-2 letter gain. Patients should be assessed regularly.

Although not as effective, patients may also be treated with one dose every 3 months after 4 monthly doses. Compared with continued monthly dosing, dosing every 3 months over the next 9 months will lead to an approximate 5-letter (1-line) loss of visual acuity benefit, on average. Patients should be assessed regularly.

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## NORSE EIGHT (ONS-5010)

- Back to the drawing board
  - Second required trial
- Non-inferiority study-newly diagnosed nAMD
- 1:1 randomization of 1.25mg ONS-5010 or 0.5mg ranibizumab
- Inject at day 0, week 4, and week 8
- Primary endpoint: mean change in BCVA from baseline to week 8
- ONS-5010 did not meet pre-specified endpoint of non-inferiority (week 8) vs. ranibizumab 0.5mg (BCVA): +4.2 letters vs. +6.3 letters
  - BUT-non-inferior at week 12

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## NORSE EIGHT (ONS-5010)

- CRL received August 28, 2025
  - "Lack of substantial evidence of effectiveness"
- Now—requesting confirmatory data
- PDUFA December 31, 2025-CRL
- June 1, 2026-Resubmitted to FDA following "formal dispute resolution process"

***FDA approved for nAMD** July 24, 2026; not approved by Health Canada***

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## *Potential Impact?*

***Drug Quality and Security Act (2013) includes the "Compounding Quality Act"***

***Expressly prohibits facilities from compounding a "copy of one or more approved drugs"***

***Estimated cost increase: $90 vs. $900 (2019)***

***Patient responsibility $18 vs. $190.80***

Zhang. Ophthalmology. 2023

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## ANYTHING OTHER THAN INTRAVITREAL INJECTIONS?

- APX3330 oral tablet for the management of diabetic retinopathy
  - Targets apurinic/apyrimidinic endonuclease 1/redox effector factor-1 (APE1/Ref-1) protein = reduction of abnormal new vessel formation (reduces VEGF & VEGF signaling) & inflammation (reduces TNF alpha)
- RZ402 oral monotherapy for DME with mild to moderate NPDR
  - Plasma kallikrein inhibitor (PKI)
  - Inhibits activation of kallikrein, blocks bradykinin
    - Blocks vasodilation, and inflammation
  - 50,200,400mg or placebo once daily x 12 weeks
- ~~OCS-01 (DME)~~ ***May 29, 2026: Primary endpoint was not met***
  - DIAMOND Phase 3 trial; topline data Q2 2026
  - Proprietary dexamethasone 6 times daily for 6 weeks vs vehicle; then 3 times through 52 weeks

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## ADENO-ASSOCIATED VIRUS-BASED STRATEGIES

- **1) AAV serotype**
  - Wild-type, recombinant, engineered capsids, self-complementary
- **2) Expression cassette**
  - Single gene, multigenic, promotors, regulatory elements, gene editing, silencing
- **3) Therapeutic target**
  - Angiogenesis, inflammation, complement system, BRB integrity, neurodegeneration
- **4) Delivery route**
  - Subretinal
  - Suprachoroidal
  - Intravitreal

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## OPTIC & LUNA TRIALS (IXOBEROGENE SOROPARVOVEC) IXO-VEC

- September 2018-FDA awarded fast track designation to a gene therapy for exudative AMD
- Aflibercept coding sequence + adenoviral associated vector (ADVM-022)
  - 30 patients
- Coding sequence (cDNA) injected ***intravitreally***
  - Replicates in deep retina producing detectable 'aflibercept' protein in vitreous, deep retina, and choroid
- Protein expression detectable for at least 4 years (laboratory data)
- Phase 3 underway, full enrollment expected Q4 2025 (at least 284 subjects)

Khanani AM, Boyer DS, Wykoff CC, Regillo CD, Busbee BG, Pieramici D, Danzig CJ, Joondeph BC, Major JC Jr, Turpcu A, Kiss S. Safety and efficacy of ixoberogene soroparvovec in neovascular age-related macular degeneration in the United States (OPTIC): a prospective, two-year, multicentre phase 1 study. EClinicalMedicine. 2023 Dec 22;67:102394.

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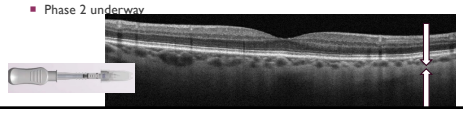
## SUPRACHOROIDAL DRUG DELIVERY

- Suprachoroidal space: potential space-higher drug concentration, increased bioavailability, prolonged duration vs. vitreous cavity
  - Triamcinolone acetonide 40mg/mL-approved 2021 for macular edema associated with uveitis
- AAVIATE (nAMD) & ALTITUDE (DR) suprachoroidal delivery of ABBV-RGX-314 (anti-VEGF antibody fragment)
  - Phase 2 underway



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## VOROLANIB (CENTER INVOLVING DME) EYP-1901

- Tyrosine kinase inhibitor: Blocks VEGF receptors intracellularly
  - Also inhibits IL-6 mediated inflammation through all JAK receptors
- Phase 2: 6-month data (VERONA)
- Phase 3
  - COMO and CAPRI (DME), LUGANO and LUCIA (nAMD)
  - Treatment every ***6 months***
  - DURAVYU 2.7mg vs. aflibercept 2mg
- 22g needle

***+ Axitinib (Phase 3)***
***25g***

**August 17, 2026- failed to meet primary efficacy endpoint! nAMD**

Butler ETS, Bjerager J, Eriksen NS, Hajari JN, Schneider M, Faber C, Subhi Y. Effect of Needle Gauge Size on Pain During Intravitreal Anti-VEGF Injection: A Systematic Review and Network Meta-Analysis. Ophthalmol Ther. 2024 Mar;13(3):801-817.

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## SUBCUTANEOUS TREATMENT

- Elamipretide-subcutaneous injection (daily..ugh) investigated in dry AMD (40mg)
  - Reduces oxidative stress at the level of **mitochondria**
    - Acts as a mitochondrial protector
      - Did not meet primary endpoints (May 2, 2022)—but enhanced ellipsoid zone preservation on OCT
        - Shows proof of proposed mechanism
    - Moving into a phase 3 trial with EZ attenuation as a surrogate endpoint
- ***All about oxidative stress***

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## BOTTOM LINE

- Therapeutic innovations in eye care are changing the way ocular disease is managed
  - Treatment targets and treatment modalities are rapidly evolving
- Ensuring access to the most effective medications in a particular clinical circumstance begins with understanding available options
- The role of regulatory powers, including the FDA is continuing to adapt to environmental circumstances

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## BOTTOM LINE

- Further developments aim to:
  - Identify new treatment targets
  - Reformulate existing agents
  - Develop alternative routes of administration
  - Increase the amount of time between treatments
  - Reduce cost of treatment
  - Improve patient quality of life

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## THANK YOU!


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