THERAPEUTIC INNOVATIONS: THE GAME CHANGERS

JESSICA STEEN OD, FAAO

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FINANCIAL DISCLOSURES

- None.

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Making an Impact

Filling an unmet need

Common conditions

Rare disease

Providing additional options

Novel products

Repurposed molecules

3

Framework for Development

Orphan drug designation (1983)

<200,000/year
Federal grants and contracts to support clinical trials
Tax credits-25% of clinical testing costs (reduced from 50% in 2018)
Exclusive right to market the drug for 7 years from date of marketing approval
Maximum flexibility to the design of pivotal trials
More likely to be single arm trials, un-blinded and use surrogate endpoints

Fast Track Designation (1988)

Drugs which fill an unmet clinical need
More frequent communication with FDA
Rolling review
Eligible for accelerated approval and priority review
Surrogate measures
2 tiered system-standard (10 months) vs. priority (6 months)

4

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?

Application fee: $3,117,218 (2022) + program fee ($369,413)
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?

Medscape OPHTHALMOLOGY MedPulse **Eyewire News**

More Medical Schools Build Training in Transgender Care
Students and faculty identify gaps, such as a severe shortage of transgender instructors, and expan goals for training.
Medscape Medical News, April 14, 2022 4

Sanctions Against Russia Are Slowing Medical Progress
Risking arrest and persecution, thousands of Russian scientists and science journalists are coming together to oppose the war and ask for professional aid.
WebMD Health News, April 14, 2022 5

Researchers Pinpoint Causes of Foveal Hypoplasia
This may allow clinicians to make quicker and more accurate diagnoses and prevent some complications.
Medscape Medical News, April 14, 2022

04.13.2022
Study Lays Foundation for Establishing Base Editing as a One-Time, Durable Treatment for Inherited Retinal Degeneration

04.13.2022
ProQR Announces Additional Sepofarsen Illuminate Trial Analyses and Provides Update on Company Strategy
Source: ProQR Therapeutics

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uticals

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BREAK DOWN

- IOP raising agents
- IOP lowering agents
- Anterior segment
- Posterior segment

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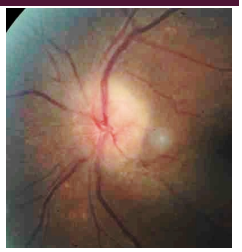
CASE

- 72 year old female
- Woke up with vision loss in the left eye yesterday morning
  - No ocular medications, no systemic medications
  - No headache, scalp tenderness, nausea, malaise, change to appetite
- BCVA: 20/25 OD; CF @ 2 ft OS
  - 3+ APD OS
- PCIOL OU, IOP 12mmHg OD and OS



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NOW WHAT?

- Unilateral disc edema
  - DDx? ***First, think "where?"…then "what?"***
    - Optic neuritis
    - GCA
    - Medications (i.e. sildenafil, amiodarone)
    - Compressive, infiltrative optic neuropathy
    - Neuroretinitis
    - Impending CRVO
    - NAION

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NOW WHAT?

- Does this patient need:
  - 1) Emergent laboratory evaluation
    - *Tests?*
      - *CBC with differential, CRP, Sed Rate (ESR)*
  - 2) Emergent neuroimaging

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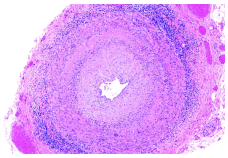
GIANT CELL ARTERITIS

- Idiopathic, **multisystem** inflammation
  - Affects medium and large vessels (internal elastic lamina)
- Upregulation of **IL-6** pathway
  - Infiltration by T cells, macrophages, histiocytes, plasma cells, multinucleate giant cells
  - Leads to occlusion and collapse of the vessel lumen = **ischemia**



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GCA TREATMENT

- **Steroids**
  - Typical initial pulse (methylprednisone 1-2g/day IV)-**inpatient**
  - Then 60-100mg prednisone daily by mouth—may be for 2+ years!
  - *Need to keep ESR down*

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WHAT'S THE TROUBLE WITH LONG-TERM STEROIDS?

- **Significant ocular and systemic side effects**
  - Cataract
  - Elevated blood pressure
  - Blood glucose dysfunction
  - Gastrointestinal ulceration
  - Fluid retention
  - Weight gain
  - Osteoporosis
  - Neuropsychiatric effects including changes in mood

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IN MEDICINE, IN GENERAL

- The trend is towards providing 'precision-based medicine'
- Steroids act to suppress the entire immune system
- Biologic agents have a specific therapeutic target in the inflammatory cascade

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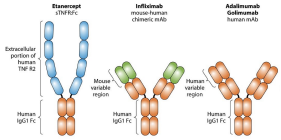
BIOLOGIC AGENTS

- Bioengineered complexes that alter the expression of components of the immune system
- Include monoclonal antibodies
  - Attach to a specific antigen on the surface of an affected cell



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ACTEMRA

- Tocilizumab 126mg/0.9mL
  - Subcutaneous injection (or intravenous infusion)
  - Weekly injection + steroid taper
- Reduces steroid load in GCA treatment
  - Also approved for RA, JIA, cytokine release syndrome

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A LITTLE LESS NEW: HUMIRA

- Adalimumab
- Subcutaneous injection
  - 80mg loading dose
  - 40mg subcutaneous injection every 2 weeks
- Approximately $5000/carton (2 pens)
- FDA approved June 2016 for the treatment of non-infectious intermediate, posterior, and panuveitis
  - Patent expires in USA in 2023
    - Already 5 FDA approved biosimilars
  - $20B last year
  - Allergan was acquired by Abbvie in May 2020

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BIOSIMILARS

- Analogous to biologics as generic medications are to branded small molecule drugs
- Biologic agents are large molecules (i.e. 150,000 Daltons vs. netarsudil 453 Da)
  - 3D structure is complex!
  - Produced from living molecules
- Goal is to be a lower-cost alternative (usually 15-30% of originator biologic)
  - But—manufacturing process is more complicated than for generic medications
  - Drugs need to be prescribed (cannot be substituted)—requires marketing to physicians

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ADVERSE EFFECTS OF TNF ALPHA INHIBITORS

- Unmasking or induction of multiple sclerosis
  - Intermediate uveitis is associated with development of MS
- Reactivation of viral hepatitis, tuberculosis
- "Lupus-like syndrome"
  - Autoantibody formation
- Possible increased risk of lymphoma
  - Medical vs. systemic disease?

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PRIOR TO INITIATION OF THERAPY

- Patients will undergo complete physical examination
  - Complete blood count with differentiation, complete metabolic panel
  - Purified protein derivative testing (or **Quantiferon gold**) and chest radiograph
  - MRI of brain to rule out demyelinating disease in some cases (intermediate uveitis)

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WHILE UNDERGOING THERAPY

- CBC with differential and metabolic panel
  - Monthly for the first three months
  - Then typically, every 2-4 months

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NEW OCULAR STEROIDS

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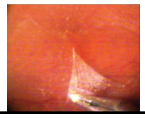
NOT-NEW: INJECTABLE STEROIDS

- 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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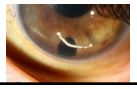
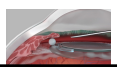
INJECTABLE STEROIDS

- 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





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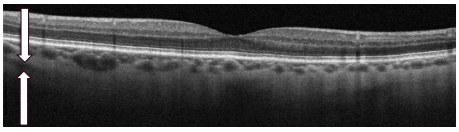
Retinal Disease

Alternative routes of drug delivery

Suprachoroidal space

Triamcinolone acetonide injectable suspension 40mg/ml (Xipere)



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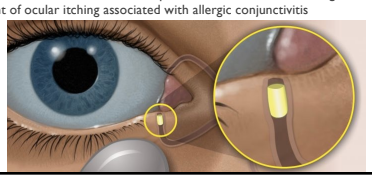
STEROID INSERT

- 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
- Utilized PDUFA (prescription drug user fee act)-deadline date for review is provided by the FDA

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AS WE GET INTO TOPICAL OCULAR FORMULATIONS…

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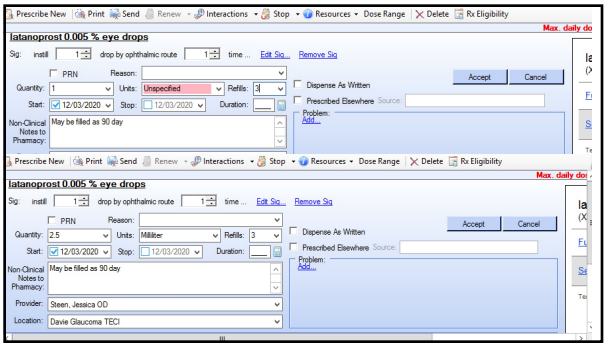

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DROP SIZE

- Drop size?
  - **Solutions:** 20 drops per mL = 50µL per drop (0.05mL)
  - 2.5mL bottle (latanoprost QHS OU) = 50 drops = 25 day supply
  - **Suspensions** (i.e. brinzolamide 1%, Azopt-10mL or 15mL, Simbrinza 8mL)
    - 15 drops per mL = 66.67 µL (0.06667mL) per drop
    - 10mL bottle = 150 drops/10mL (TID) = 50 day supply; or 25 days OU
    - 8mL bottle = 120 drops/8mL (TID) = 40 day supply; or 20 days OU

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SO WHAT?

- Tear film volume 7µL, max capacity of the conjunctival sac 30µL (without blinking)
  - 15µL/drop is proposed to be an 'ideal' drop volume
- What about wasted medication?
  - $$$
- Drop size was approved by the FDA; bottle redesigns will need FDA approval
  - Cost is likely to be passed on to patients

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Bottle Design and Drop Size

Plant-derived eye drop bottle

Sugarcane-derived material

Many droppers release upwards of 30µL per drop-also depends how you hold the drop!

Manufacturers tend to overfill bottles

Significant variation

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IOP LOWERING AGENTS

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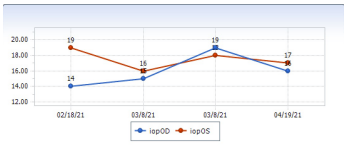
56 YEAR OLD AFRICAN AMERICAN FEMALE

- 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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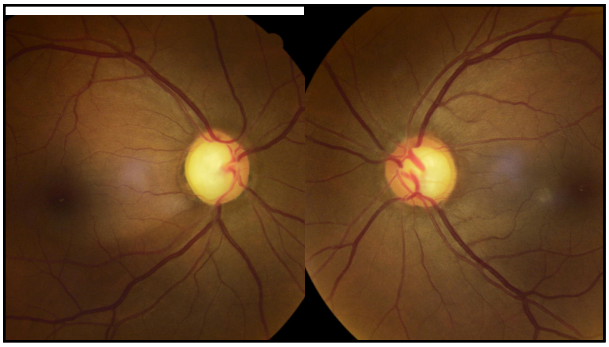

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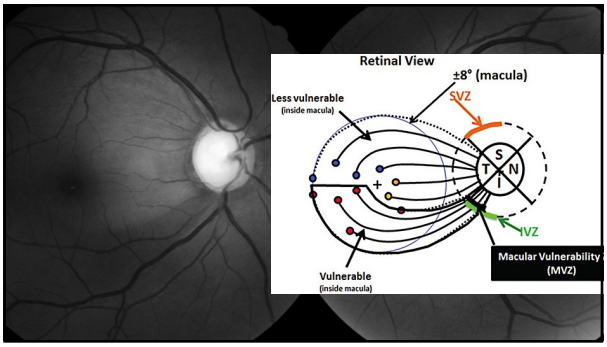

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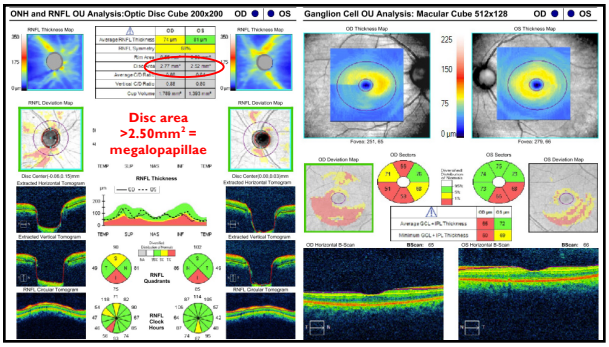

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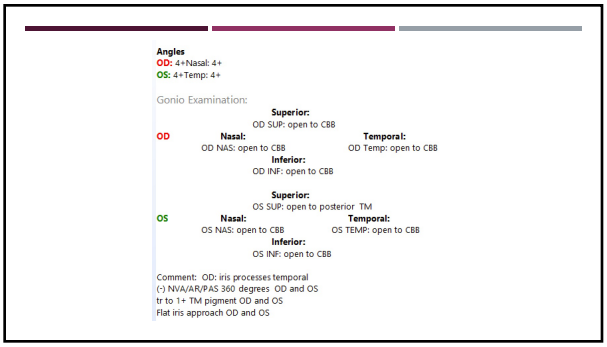

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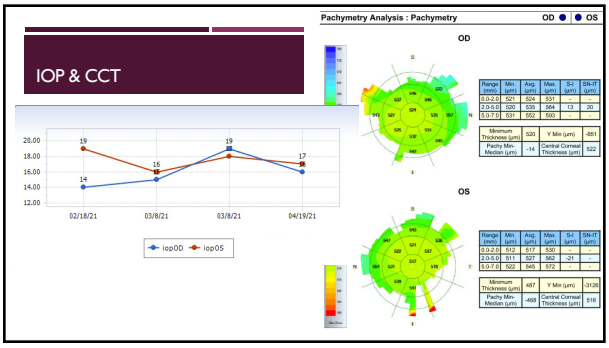

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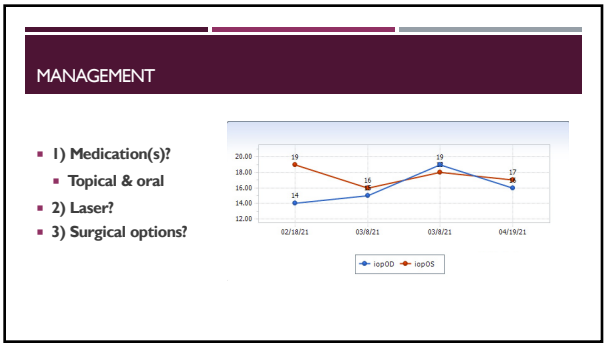

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IOP LOWERING MEDICATION OPTIONS

- 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 ophthalmic emulsion 0.005% (Xelpros)
  - BAK-free—uses a different preservative: potassium sorbate 0.47%
    - BAK can decrease goblet cell density
  - *Not available from pharmacies*
  - *Uses a "direct pay" method*

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DIRECT PAY EXAMPLE

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Latanoprost Drops

MD: **JESSICA STEEN OD**

3200 S UNIVERSITY DR

DAVIE, FL 33328

Express Scripts manages the prescription drug benefit for your patient at the request of their plan sponsor. Your patient's prescription benefit requires that we review certain requests for coverage with the prescriber. You have prescribed a medication for your patient that requires Prior Authorization before benefit coverage or coverage of additional quantities can be provided. Please complete the following questions then fax this form to the toll free number listed below. Upon receipt of the completed form, prescription benefit coverage will be determined based on the plan's rules.

SECTION A Please answer the following questions *(Please fill in the entire circle which corresponds to your answer for each question)*

1. What is the indication or diagnosis?
   - Reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension. Note: Open-angle glaucoma includes normal-tension glaucoma, which is also referred to as low-tension glaucoma or normal-pressure glaucoma.
   - Cosmetic conditions (for example, eyelash growth)
   - All other indications or diagnoses

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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

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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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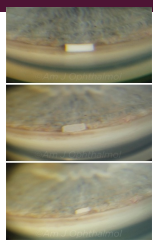
SUSTAINED RELEASE AGENTS



- Durysta (bimatoprost implant 10mcg)
  - Sustained release bimatoprost
    - Equivalent to about 2-3 drops of Lumigan
    - Drug release complete in 3-4 months
  - Effect lasts about 6 months (may be longer)…Extension of the ARTEMIS trial
    - ARTEMIS 1 and 2-Implant on day 1, week 16, week 32
      - Endpoint studied at end of week 12
  - No eyelash growth, no redness
  - Iris change? Probably not

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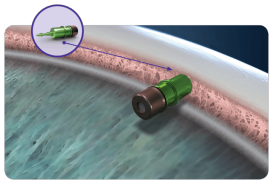
SUSTAINED RELEASE AGENTS



- iDose
  - Titanium implant (travoprost)
  - Phase 3 trial underway
  - Not refillable

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ANTERIOR SEGMENT MEDICATIONS

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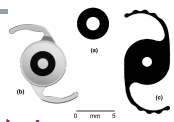
Presbyopia

Pinhole effect



Small aperture = reduced spherical aberration, increased depth of focus

Pilocarpine 1.25% ophthalmic solution

FDA approved October 30, 2021

Currently under investigation:

Phentolamine 0.75% + pilocarpine 0.4%
Brimonidine + carbachol
Pilocarpine
Pilocarpine 0.302% + phenylephrine 0.624% + pheniramine 0.0772%

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PILOCARPINE 1.25% (VUITY)

- Presbyopia is a "prevalent and degenerative eye illness"
- Cholinergic muscarinic agonist indicated for the treatment of presbyopia in adults
  - Constricts the pupil-but maintains some response to light
- Preserved with BAK
- Pilocarpine initially FDA approved in 1974
- pHast technology
  - Adjusts to physiological pH of tear film—improves comfort and solubility

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GEMINI 1 AND GEMINI 2

- 750 individuals (40-55 years of age)
  - Once daily dosing
- Met endpoints vs. vehicle on day 30 at **hour 3** at day 30
- Statistical significant improvement in near vision in mesopic conditions
  - 3 lines at near or more in mesopic, high contrast, binocular distance corrected near visual acuity without losing more than 1 line of corrected distance visual acuity
- Intermediate vision improvement up to 10 hours after instillation
- Most common adverse effects:
  - Headache (15%), hyperemia (5%), blurred vision (5%)

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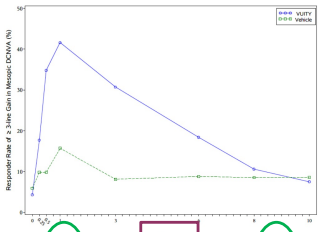
Figure 1: Proportion of Participants Achieving 3-Lines or More Improvement in Mesopic, High Contrast, Binocular DCNVA at Day 30 in GEMINI 1 (Intent-to-Treat Population)



Timepoint	Hour 0	Hour 0.25	Hour 0.5	Hour 1	Hour 3	Hour 6	Hour 8	Hour 10
VUITY (%)	4.3	17.7	34.8	41.6	30.7	18.4	10.6	7.5
Vehicle (%)	5.9	9.8	9.8	15.7	8.1	8.8	8.5	8.6
Difference (95% CI)	-1.5 (-6.4, 3.3)	7.9 (0.3, 15.5)	25.0 (16.2, 33.8)	25.9 (16.4, 35.5)	22.5 (14.3, 30.8)	9.7 (2.3, 17.0)	2.1 (-4.4, 8.5)	-1.1 (-7.1, 5.0)

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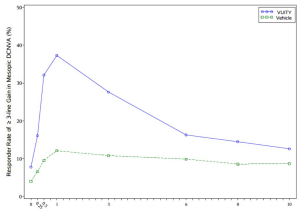
Figure 2: Proportion of Participants Achieving 3-lines or More Improvement in Mesopic, High Contrast, Binocular DCNVA at Day 30 in GEMINI 2 (Intent-to-Treat population)



Timepoint	Hour 0	Hour 0.25	Hour 0.5	Hour 1	Hour 3	Hour 6	Hour 8	Hour 10
VUITY (%)	7.8	16.1	32.1	37.3	27.6	16.3	14.5	12.6
Vehicle (%)	4.0	6.6	9.6	12.1	10.8	9.9	8.6	8.7
Difference (95% CI)	3.8 (-0.9, 8.4)	9.4 (3.2, 15.7)	22.5 (14.7, 30.3)	25.2 (17.0, 33.4)	16.7 (9.1, 24.3)	6.5 (-0.1, 13.1)	5.9 (-0.5, 12.2)	3.8 (-2.3, 10.0)

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ANYTHING ELSE?

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Presbyopia

Soften the lens

Lipoic acid choline ester 1.5% (UNR844)
Currently under investigation

Reduces disulfide bonds between lens proteins and restore natural ability to accommodate

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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

Demodex blepharitis

Lotilaner ophthalmic solution 0.25% (TP-03)
Currently in phase 3 clinical trials

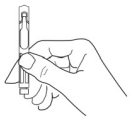
Demodex is more common than we think

Antiparasitic agent

65

UPNEEQ

- Oxymetazoline hydrochloride solution 0.1%
  - Alpha-1 adrenergic agonist
- For the treatment of acquired blepharoptosis
- Direct pay model: one pharmacy-no insurance
- Once daily dosing



	Package Price (incl. shipping/handling)	Effective Monthly Price
90 ct	$225	$75 (–30% Savings vs 30 ct)
30 ct	$105	$105

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OXERVATE

- Cenegermin 0.002% (20mcg/mL)
  - Recombinant human nerve growth factor
- FDA approved August, 2019 for the treatment of neurotrophic keratitis
- 6x daily for 8 weeks
- *What do you think the most common adverse effect was in the pivotal trial?*
  - *39.1% reported ocular events*

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THYROID EYE DISEASE

- What types of thyroid disease are most likely to cause Graves disease?
- **Autoimmune thyroid disease**
- Autoantibody and autoantigen formation in the orbit leads to production of cytokines (proinflammatory) → activate T lymphocytes → activate orbital **fibroblasts** → proliferate hyaluronan which leads to soft tissue expansion = thyroid eye disease

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TEPROTUMUMAB (TEPEZZA)

- Monoclonal antibody
  - Targets insulin like growth factor 1-binds to IGF-1R and blocks its activation
  - Fibroblasts often have IGR-1R
    - Autoantibodies have no binding site!
- Intravenous infusion-series of 8 treatments over 24 weeks
  - Every 3 weeks

Autoantibody and autoantigen formation in the orbit leads to production of cytokines (proinflammatory) → **activate T lymphocytes** → activate orbital fibroblasts → proliferate hyaluronan which leads to soft tissue expansion = thyroid eye disease

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MYASTHENIA GRAVIS

- Efgartigimod (Vygart) FDA approved December 17, 2021
  - Generalized MG who test positive for the anti-acetylcholine receptor (AChR) antibody
- Antibody fragment which binds and blocks recycling of IgG. Reduces IgG levels—including the abnormal AChR antibodies
- *Fast track designation & orphan drug designation*

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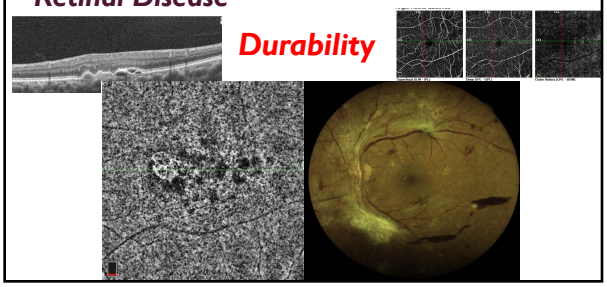
Retinal Disease

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
PIGF

TKI pathways

TIE2 activation pathways

Integrin pathways

Gene therapy

Unmet needs in management of retinal disease?

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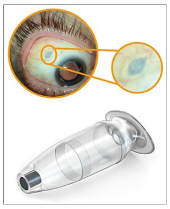
PORT DELIVERY SYSTEM WITH RANIBIZUMAB

- Permanent, reusable, surgically-'placed' reservoir
- 3.5mm pars plana incision
- Holds 20 µL of custom formulation of ranibizumab
  - Phase 2: LADDER → PORTAL
  - Phase 3: ARCHWAY
    - Refill every 6 months
    - Met primary endpoints
      - 10.7 injections in ranibizumab arm vs. 2 fills



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ADVERSE EFFECTS OF ANTI-VEGF INJECTIONS

- Subconjunctival hemorrhage
- Increased intravitreal volume
  - Increased intraocular pressure
    - Acutely—and long term
- Risk of endophthalmitis
  - Approximately 1/2659 injections
    - Role of topical antibiotic prophylaxis?
- Risk of retinal detachment, vitreous hemorrhage
- Stroke, myocardial infarction-conflicting data

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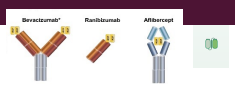
BEOVU



- Brolucizumab (Beovu)-approved October 8,2019
  - Single chain antibody fragment inhibitor of VEGF
  - Molecular weight half of ranibizumab
    - Smaller molecule = improved penetration, faster clearance, lower systemic exposure
  - Phase 3 trials-top line results
    - HAWK/HARRIER trials showed non-inferiority to Eylea in visual acuity and fluid reduction in patients with wet AMD
    - Improved acuity vs. aflibercept
    - Improved central thickness and fluid on OCT vs. aflibercept
  - **12 week duration (after 3 monthly loading doses) for nAMD**
  - **On label for neovascular AMD;** *KITE and KESTREL (DME) in progress,* ~~*RAPTOR and RAVEN & MERLIN*~~

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BEOVU

- February, 2020: 14 cases of vasculitis (11 were occlusive retinal vasculitis)
  - As of March 13, 2020: more than 65,000 injections
  - Through June 26, 2020
    - 7.92 events/10,000 injections (retinal vasculitis, retinal vascular occlusion-or both)
      - As high as 4% incidence of inflammation; and 0.7% of IOI and loss of 15+ letters
- *Contraindicated in patients with active intraocular inflammation*
  - *But…so is Eylea*

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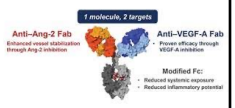
FARICIMAB (VABYSMO)

- FDA approved January 28, 2022-the newest! **(currently)
- Bispecific antibody
  - 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)



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COST EFFECTIVENESS OF ANTI-VEGF

- $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
- $60 bevacizumab (1.25mg/0.05mL)-Avastin

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

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WHILE WE'RE SPEAKING ABOUT BEVACIZUMAB

- Bevacizumab-vikg (Lytenava)
  - BLA submitted March 31, 2022
  - Anticipated approval late 2022 or first quarter 2023
- 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?***

----------DOSAGE AND ADMINISTRATION----------
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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RETINAL BIOSIMILARS

- **The first:**
- Ranibizumab-nuna (Byooviz) FDA approved September 17, 2021
  - nAMD, macular edema following RVO, and myopic choroidal neovascularization
  - Launch expected Summer 2022

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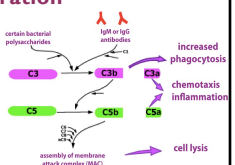
Retinal Disease

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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COMPLEMENT INHIBITORS IN GA

- ***Geographic atrophy doesn't get better-the goal is to slow progression***
- APL-2 (Pegcetacoplan)-C3 inhibitor
- Met phase 2 endpoints (FILLY) in September 2019-slows GA rate of progression **in a dose-dependent manner**
- Phase 3 trials (DERBY & OAKS)
  - Endpoints met in OAKS, very close in DERBY
  - Pooled data met endpoints
- **Slows the growth rate of geographic atrophy**
- *Fast track designation from FDA (GA)-Unmet clinical need*
  - *Interesting safety signal: increased risk of exudation*
- ***Whatever drives a druse towards GA is the same mechanism that seems to cause GA expansion***

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COMPLEMENT INHIBITION IN GEOGRAPHIC ATROPHY

- C5 inhibitor
  - Zimura (Avacincaptad pegol)
    - Seems to protect mitochondria from oxidative damage
- Phase 3 (GATHER1)-October 28, 2019-met primary endpoints (reduction in growth rate of GA at month 12)
  - Also being investigated in Stargardt's disease
- Phase 3 (GATHER2) began June 30, 2020, topline results expected Q3, 2022
  - Phase 3 trial for intermediate stage dry AMD to begin late 2022
- *Awarded fast-track designation from FDA*

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GEOGRAPHIC ATROPHY

- Elamipretide-subcutaneous injection (daily..ugh)
  - 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**
- Risuteganib (Luminate)
  - Also investigated in DR
  - Anti-integrin therapy
- ***All about oxidative stress***

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GENE THERAPY IN RETINAL DISEASE

- Gene augmentation
  - A specific wild-type allele of a gene of interest is inserted using a viral (adenoviral associated) vector
  - Allows expression of 'normal' gene product
- Luxturna (voretigene neparvovec-ryl) FDA approved 2017
  - RPE-65 biallelic mutation
  - Injected subretinally (performed in an OR)
  - AAV-2 vector
  - *5 year data recently released*

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OPTIC TRIAL-ADVM-022

- 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
- May last up to 2 years
- Durability up to 92 weeks (cohort 1-high dose)
  - High dose vs. low dose; 13 day oral steroid vs. 6 week topical ophthalmic steroid
- ***Next step: initiate a pivotal trial***
  - ***Anticipated first patient to be dosed Q3 2022***

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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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