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## Mark Dunbar: Disclosure

- Optometry Consultant/Advisory Board
  - Carl Zeiss
  - Allergan
  - Regeneron
  - Genentech
  - Tarsus
  - Orasis
  - Iveric
  - Apellis

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## Hot Topics in Retina

- New Treatments for GA
- Better Treatments for Wet AMD
- Vuity
- Targeted therapy for hereditary retinal disease
- Is vitrectomy a reasonable option for floaters?

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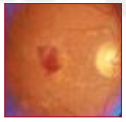
## Age-related Macular Degeneration (AMD)

- Degenerative disorder that affects the macula
- Leading cause of legal blindness in people > 65 yo
- 90% of vision loss is 2º to CNV

- Patients Affected
  - 90% dry or nonexudative
  - 10 % wet or exudative
- VA < 20/200
  - 80-90% exudative
  - 10-20% dry



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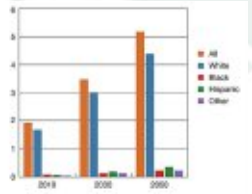
## AMD "Factoids"

- 1 in 3 people older then 75 will be affected by AMD
  - The number of people > 75 is steadily increasing
  - 10,000 people turn 65 in the US every day
- By 2025, there will be **44%** more people in the US in this "high-risk" age group than there are today
- UN: people over age 60 will triple: 606 million worldwide to nearly a billion by 2050 (33%)

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## Neovascular AMD: Risk Factors

- Emerging risk factors
  - Age[1]
  - Race[1]
  - Smoking[2]
  - Family history[3]
  - Variation in the complement factor H gene[4-6] and other genes[7]

1. Friedman et al. *Arch Ophthalmol.* 2004;122:564; 2. Kahn et al. *Br J Ophthalmol.* 2006;90:75; 3. Buch et al. *Acta Ophthalmol Scand.* 2005;83:409; 4. Hageman et al. *Proc Natl Acad Sci USA.* 2005;102:7227; 5. Haines et al. *Nat Genet.* 2005;37:1355; 6. Klein et al. *Science.* 2005;308:385; 7. Seipp et al. *Invest Ophthalmol Vis Sci.* 2006;47:536; 7. Haines et al. *Invest Ophthalmol Vis Sci.* 2006;47:329.

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## What We Now Know

- Genetic background
- Environmental/lifestyle risk factors
- The interaction between these variables, predispose to AMD
- Treatments for wet AMD target VEGF
  - Hugely successful
- The future of AMD will target dry AMD

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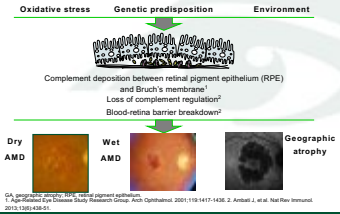
## Current Hypothesis for AMD Pathophysiology




GA, geographic atrophy; RPE, retinal pigment epithelium.
1. Age-Related Eye Disease Study Research Group. Arch Ophthalmol. 2001;119:1417-1436. 2. Ambati J, et al. Nat Rev Immunol. 2013;13(6):438-51.

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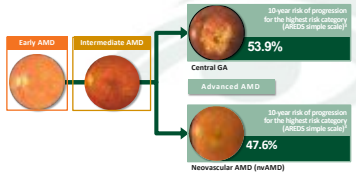
## AMD Is the Leading Cause of Blindness for Caucasians in the US[1]




AMD, age-related macular degeneration; AREDS, Age-related Eye Disease Study; GA, geographic atrophy; nvAMD, neovascular AMD.
1. Eye Diseases Prevalence Research Group. Arch Ophthalmol. 2004;122(4):477-485. 2. Ferris FL, et al. Ophthalmology. 2013;120(4):844-851. 3. Chew EY, et al. JAMA Ophthalmol. 2014;132(3):272-277. 4. Age-Related Study Disease Study Research Group. Arch Ophthalmol. 2005;123(11):1570-1574.

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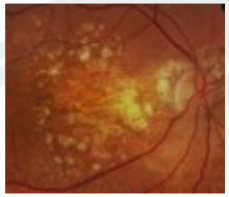
## Geographic Atrophy

- Advanced/late form of dry AMD
- Atrophy of the RPE and photoreceptors



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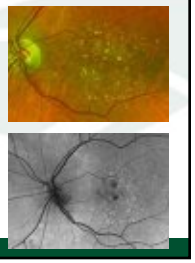
## Is GA More Common Than We Thought?

- We haven't been looking for it
  - In part because there was no treatment
- The focus has been detecting the conversion from dry to wet
- Often starts extrafoveal and small
  - Unless you are looking for it – you may not realize that it is present



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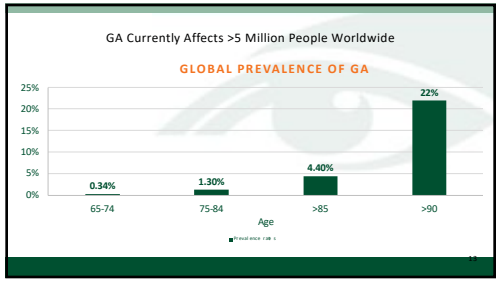


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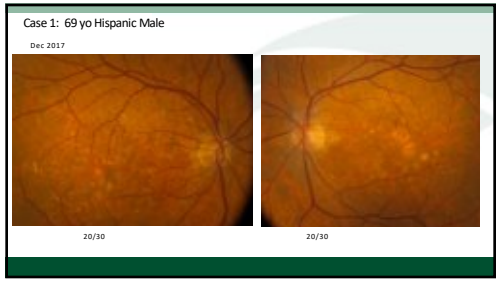


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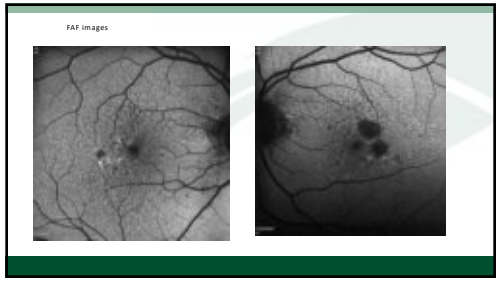


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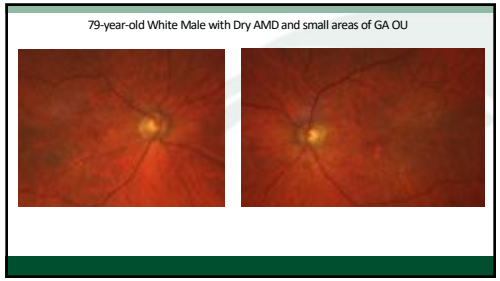


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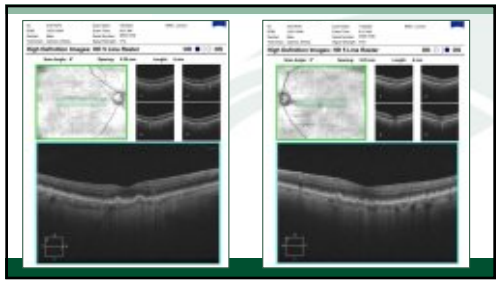

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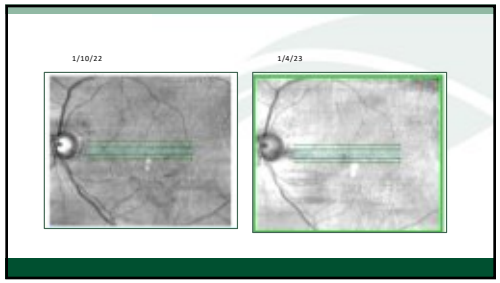


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## Geographic Atrophy Impact on Quality of Life

- **Global Geographic Atrophy Insights Survey (GAINS)**
  - Sponsored by Apellis Pharmaceuticals and conducted by The Harris Poll last year
    - Included 203 adult participants with GA, in 9 countries
  - **7 in 10** believe the impact on their independence and quality of life due to visual decline is worse than they expected
  - **Majority felt** the disease negatively affects their ability to read, drive, and travel;
  - **1 in 3 recently withdrawn from social activities** due to their disease

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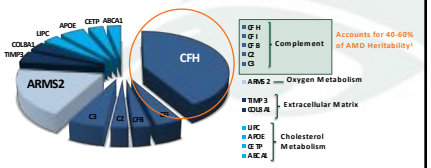
## Key Genes Involved in the Development of AMD




1. Fritsche LG, Fariss RN, Stambolian D, Abecasis GR, Curcio CA, Swaroop A. Age-related macular degeneration: Genetics and biology coming together. Annu Rev Genomics Hum Genet. 2014;15:151-171.

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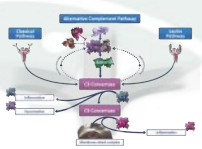
## The Compliment System

- **Complement Pathway** is one of the body's primitive defense immune systems
  - First line of defense for our immune syste
  - Made up of a group of proteins that:
    - Mounts inflammation
    - Destroys foreign invaders
    - Removes debris resulting from that destruction
- Complement Factor H is a gene that gives instructions for making Factor H
  - Factor H is an important *inhibitory regulator* of this system
- Drusen contain most all of the proteins that make up the complement system



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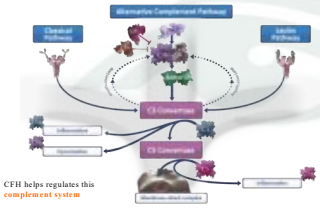
## Pathways for Complement Activation

*Required for the initiation and amplification of the alternative complement pathway*



CFH helps regulates this complement system

Figure based on the scientific information from the following sources: Owen J., Punt J. and Stranford S. (2013) Kuby Immunology 7th edition, New York: W.H. Freeman and Co Ltd; Walport MJ. N Engl J Med 2001;344:1058-66

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## Complement System and Potential GA Therapies

- The complement cascade is a strategic target for GA therapy
- The COMPLEMENT SYSTEM is first line of defense of the immune system
- It protects us from microorganisms
- It constitutes our innate immunity, which is not adaptable and does not change as we age
- Activated by the adaptive immune system (through antigen antibody interaction)

Boyer DS, Schmidt-Erfurth U, van Lookeren Campagne M, Henry EC, Brittain C. The Pathophysiology Of Geographic Atrophy Secondary to Age-related Macular Degeneration and the Complement Pathway as a Therapeutic Target. Retina. 2017;37(5):819-835.

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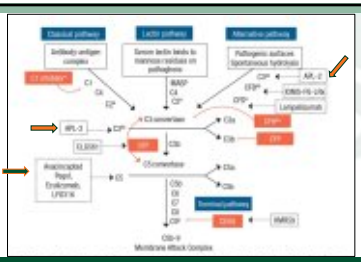

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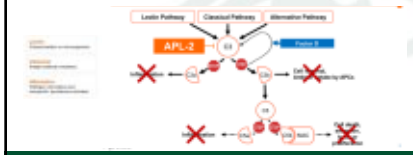
## Potential Treatments for Geographic Atrophy

- **Pegcetacoplan (Syfovre) :** C3 inhibitor by Apellis
- Blocks all the pathways of complement activation




MAC = membrane attack complex

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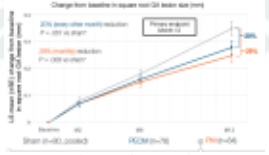
## Pegcetacoplan (Syfovre)

**Phase 3 DERBY & OAKS Objective:**
Assess the efficacy and safety of multiple intravitreal injections of pegcetacoplan in patients with GA secondary to AMD

**Phase 2 FILLY Results**



*P <0.1 was the predefined threshold for statistical significance in FILLY.
LS=least squares; M=Month; PECM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.

Liao DS, et al. Ophthalmology. 2020;127:186-95.

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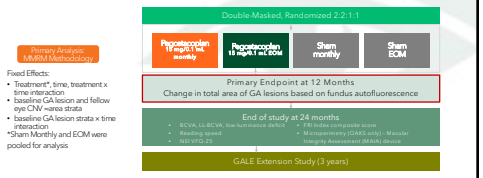
## Global Phase 3 Program: OAKS & DERBY Study Design




Primary Analysis: MMRM Methodology

Fixed Effects:
- Treatment*, time, treatment x time interaction
- baseline GA lesion and fellow eye CNV +area strata
- baseline GA lesion strata x time interaction

*Sham Monthly and EOM were pooled for analysis

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## OAKS and DERBY

**Monthly and every-other-month pegcetacoplan continued to reduce GA lesion growth at 18 months**

Pegcetacoplan showed continued and clinically meaningful reductions in GA lesion growth from baseline to month 18.

Apellis. Apellis announces pegcetacoplan showed continuous and clinically meaningful effects at month 18 in phase 3 DERBY and OAKS studies for geographic atrophy (GA). https://investors.apellis.com/news-releases/news-release-details/apellis-announces-pegcetacoplan-showed-continuous-and-clinically. Updated March 16, 2022. Accessed March 16, 2022.

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## Pegcetacoplan: Take-Away Points

- Pegcetacoplan monthly and every other month **met the primary endpoint in OAKS**
- Pegcetacoplan monthly and every other month **did not meet the primary endpoint** in DERBY
- Data at 18 months from the combined studies show the potential for improving treatment effects with pegcetacoplan over time.
- **Pegcetacoplan treatment effect accelerated between months 18-24,** demonstrating a robust reduction of GA lesion growth compared to sham

1. https://investors.apellis.com/news-releases/news-release-details/apellis-announces-plans-submit-24-month-phase-3-data#ds.

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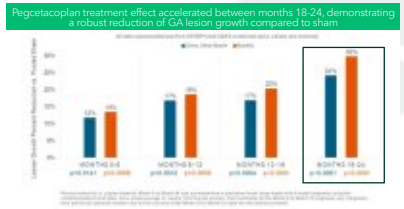
## OAKS and DERBY

**Pegcetacoplan treatment effect accelerated between months 18-24, demonstrating a robust reduction of GA lesion growth compared to sham**



https://investors.apellis.com/news-releases/news-release-details/apellis-announces-24-month-results-showing-increased-effects

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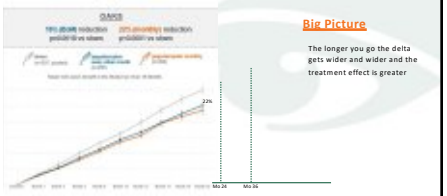
## OAKS and DERBY



Big Picture

The longer you go the delta gets wider and wider and the treatment effect is greater

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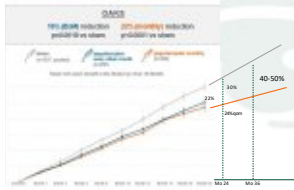
## OAKS and DERBY




Big Picture

The longer you go the delta gets wider and wider and the treatment effect is greater

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Apellis: Pegcetacoplan

Is that a significant treatment effect for GA?

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## Pegcetacoplan: Take-Away Points

- Pegcetacoplan **treatment effect accelerated between months 18-24, demonstrating a robust reduction of GA lesion growth compared to sham**
- Pegcetacoplan demonstrated greater efficacy in patients with extrafoveal lesions at baseline
- In a post-hoc analysis, after correcting for disparities in baseline characteristics, OAKS and DERBY results are more convergent
- OAKS and DERBY show consistent efficacy of pegcetacoplan in treated study eyes versus untreated fellow eyes
- Overall, pegcetacoplan administered monthly or every other month was well tolerated in patients with GA
  - Majority of IOI cases were mild, and most patients resumed IP administration
  - **6.0%, 4.1%, and 2.4% of patients in the combined PM, PEOM, and sham groups experienced new-onset investigator-determined exudative AMD**

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## Avacincaptad Pegol (Zimuria): Iveric

- Complement C5 inhibitor
- Reduction in GA growth for patients receiving Zimura in the U.S. was **25.5 - 32.0%**

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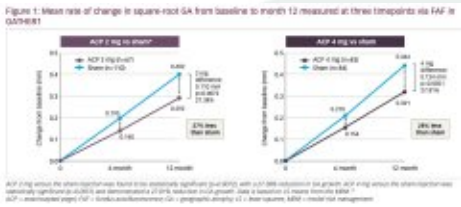

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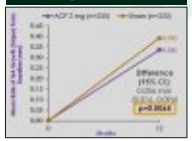
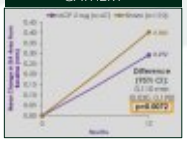
## Avacincaptad Pegol:
First Investigational GA Therapy to Achieve the 12-month Prespecified, Primary Endpoint in 2 Pivotal Phase 3 Studies

GATHER2



GATHER1



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**Cross-trial comparison of Zimura and intravitreal pegcetacoplan in geographic atrophy**

| Project (company) | Zimura (Iveric Bio) | | Intravitreal pegcetacoplan (Apellis) | | | |
|---|---|---|---|---|---|---|
| Trial | Gather2 | Gather1 | Derby | | Oaks | |
| | | | Monthly | Every other month | Monthly | Every other month |
| Change in GA area vs sham at 12mo | 14%* | 27%* | 12% | 11% | 22% | 16% |
| p value | 0.0064 | 0.0072** | 0.0528 (NS) | 0.0750 (NS) | 0.0003 | 0.0052 |
| Choroidal neovascularisations | 7%*** | 9%*** | 7%^ | 3%^ | 5%^ | 5%^ |

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## Where we are today with GA?

- An FDA approved treatment
  - By August we will likely have a 2nd Treatment
- Monthly intravitreal injection
- Takes at least ~ 12 months to show any significant therapeutic benefit
- By 18-24 months the treatment affect accelerates
- Keep in mind many patients will have good acuity

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## Anti-VEGF Standard of Care for Wet AMD

- Require frequent injections
- 1/3 of eyes develop geographic atrophy
- Significant vision loss after 5–7 years of therapy

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## Next Generation of Treatments for Wet AMD

- Beovu (Brolucizumab - Novartis)
  - Small size of the molecule allows higher dosing per volume results in a longer-lasting effect
- Vabysmo: Farcimab (Genentech)
- Port Delivery System (Genentech): Susvimo
  - Surgically implanted, refillable reservoir
  - Median time to first refill was 18 months
    - But large range: 7-8 months - 2 years

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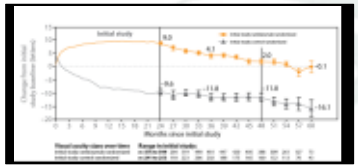
## HORIZON: Extension Study



Extension study evaluating the ≥2-year frequency, safety, tolerability, and efficacy of multiple intravitreal ranibizumab injections in Wet AMD patients who completed 1 of 3 initial studies: MARINA, ANCHOR, or FOCUS

Ranibizumab 0.5 mg was administered at the investigator's discretion

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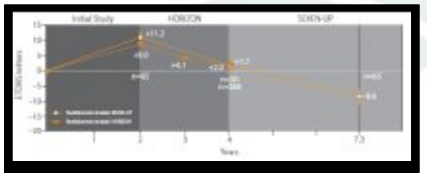
SEVEN-UP Study: 7-Year Outcomes in Treated Patients in MARINA, ANCHOR, and HORIZON

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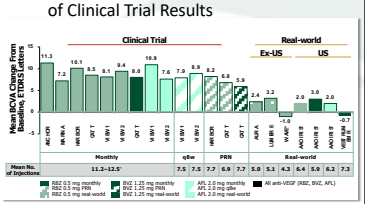
## Real-world Visual Acuity Outcomes Fall Short of Clinical Trial Results

**Clinical Trials[1-5] vs Real-world Studies[6-10]**
1-Year Outcomes With Anti-VEGF Treatment

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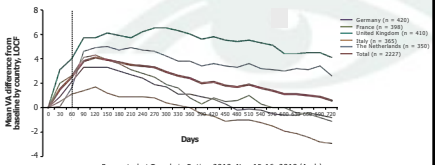
## Visual Acuity Gains Were Not Maintained After ~120 Days

- In all countries, mean VA declined following an initial improvement




Presented at Trends in Retina 2019, Nov 15-16, 2019 (Awh)

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## Tx with Broluizumab

- 50% of patients were maintained on q12 week dosing without requiring rescue treatments.
  - Eyes that could not be maintained on a regimen of q12 weeks tended to show a need for early re-treatment
- ~ 1/3 fewer patients (vs Lucentis) had fluid (IRF and/or SRF)
- At week 48, 31% fewer patients had IRF and/or SRF in HAWK, and 41% fewer in HARRIER ($P < .0001$ for both).
- Patients receiving brolucizumab 6 mg demonstrated superior reductions in central subfield thickness.

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## Beovu (Brolucizumab)

- Received FDA approval October 7, 2019 for treatment of neovascular AMD
- Shortly after approval the American Society of Retina Specialists (ASRS) began receiving reports of inflammation following intravitreal brolucizumab administration for NVAMD
- Several reported cases included **retinal vasculitis** that frequently resulted in vascular occlusion and **significant vision loss**

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2020

- On February 23, the American Society of Retinal Specialists (ASRS) shared a note with its membership stating that since approval on October 7, 2019, ASRS has received reports of 14 cases of vasculitis, of which 11 were designated as occlusive retinal vasculitis

**Novartis Responds to ASRS Note Raising Safety Concerns of Beovu**

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## Recent FDA Approvals for AMD and DME

- Port Delivery System (PDS)
- Vabysmo: Farcimab

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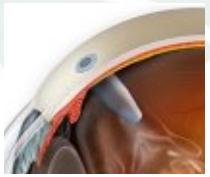
## Port Delivery System (Genentech)

- Surgically implanted, refillable reservoir
- Median time to first refill was 18 months
  - But large range: 7-8 months - 2 years



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## Port Delivery System (PDS)

- A permanent refillable eye implant that continuously delivers ranibizumab over a period of months
- Refilled every **6 months**, PDS demonstrated non-inferior and equivalent efficacy compared to the standard of care – monthly ranibizumab eye injections
- Archway Study: Phase 3 results presented July 2020
  - Port delivery equivalent to monthly Ranibizumab injections
  - 248 pts PDS vs. 167 monthly injections
  - **98% did not need supplement injection**

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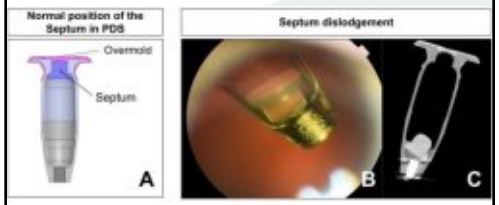
## Septum Dislodgement

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## Voluntary Recall of the PDS Ocular Implant

**October 2022**

- The manufacturer initiated a voluntary recall of the Port Delivery System with ranibizumab (PDS) ocular implant and insertion tool assembly, including the drug vial and initial fill needle.
- The recall does not include the ranibizumab 100 mg/ml drug vial for refill exchange procedures or the refill needle so that patients who have already received the PDS can continue refill exchange procedures.
  The recall also does not include the PDS explant tool.
- The US Food and Drug Administration (FDA) was informed and is aligned with the approach.

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## Reason For Recall

- An investigation into septum dislodgement cases in the PDS phase 3 clinical trial program identified a need for additional testing of the commercial implant supply.
- The additional testing involved repeatedly puncturing the PDS implants with a needle, to evaluate performance of the septum of the implant over the long-term via multiple refills. The results showed that some implants did not perform up to standards.
- As of August 31st, 2022, there have been 33 reported cases of septum dislodgement in approximately 1,419 patients with implants (2.3%, includes re-implantations) and 5,236 refill-exchange procedures (0.63%) across PDS clinical trials.

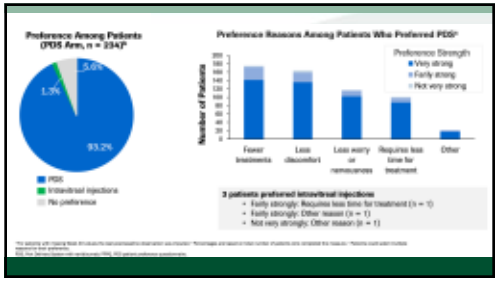
55

## Wet AMD Patients Prefer PDS Implant Over Injections

Patients underwent only 2 procedures in 40 weeks.

- Patients in Genentech's phase 3 ARCHWAY trial **strongly preferred the PDS** sustained-release implant over regular injections of ranibizumab
- > 93% of the 228 patients who received the implant cited such reasons as **fewer injections**, **reduced discomfort**, and **less nervousness** and apprehension
- Patients in injection arm averaged ~ 10 injections over 40 weeks
  - Implant had only the initial implantation in the operating room and a mandated in-office refill at 24 weeks
  - **Only 4 of 228 patients required a PDS refill prior to 24 weeks.**
- PDS with a custom formulation of ranibizumab **provided** essentially **the same efficacy as monthly injections of regular ranibizumab**

56




57

January 31, 2022

*FDA approves Roche's Vabysmo, the first bispecific antibody for the eye, to treat two leading causes of vision loss*

- Vabysmo (faricimab-svoa) targets and inhibits two disease pathways that drive neovascular or "wet" age-related macular degeneration (nAMD) and diabetic macular edema (DME)
- Vabysmo is the only injectable eye medicine approved simultaneously in the US for nAMD and DME, with flexible dosing regimens based on patient need

58

## Angiopoietin/Tie-2 Signaling Pathway

*A key player in the pathogenesis of AMD and DME*

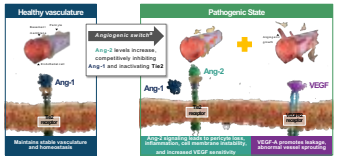
59

## The Angiopoietin/Tie2 signaling pathway maintains vascular homeostasis

- Responsible for blood vessel growth during embryonic development
- Controls vascular stability, vascular permeability, and inflammation

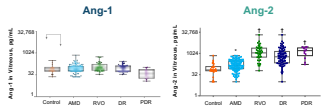

60

## Ang-2 and VEGF-A are key drivers of angiogenesis, leakage, and microvascular inflammation




61

## Ang-2 levels increased in vitreous of patients with retinal disorders



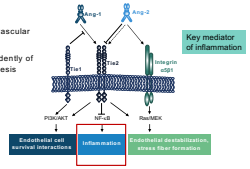

**Ang-1** is constitutively expressed regardless of disease state to maintain healthy vasculature

**Ang-2** levels are only increased under pathological conditions

62

## Ang-2 contributes to inflammatory signaling independent of Tie2

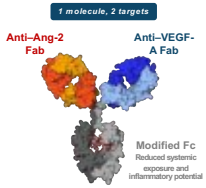
- Retinal inflammation is a key player in neovascular AMD and DME
- Ang-2 can signal through integrins independently of Tie2, promoting inflammation and angiogenesis




63

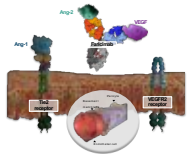
## Faricimab: first bispecific antibody designed for intraocular use

- Engineered for efficacy, duration within the eye, and fast systemic clearance




64

## Neutralizing both Ang-2 and VEGF with faricimab

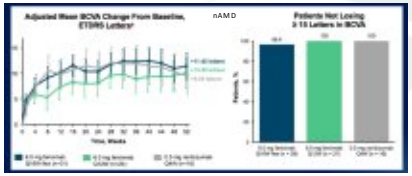



Targeting both:

- Promotes pericyte and vessel stabilization
- Reduces fluid leakage
- Reduces growth of new vessels
- Reduces inflammation

65

## BCVA Outcomes with q 16 W and q 12 W Farcimab were Comparable to q4 Ranibizumab at 52 Weeks

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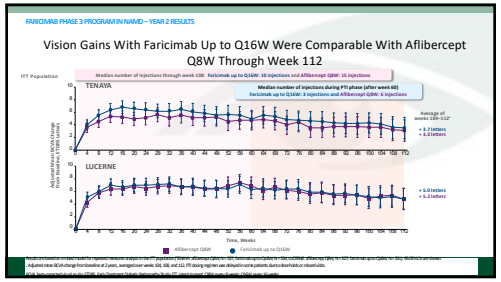


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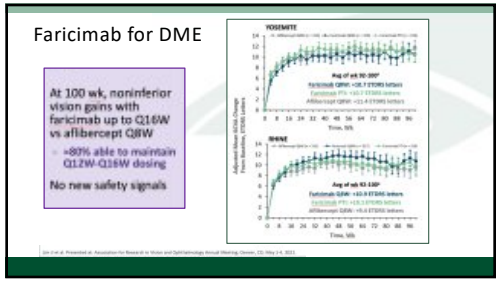


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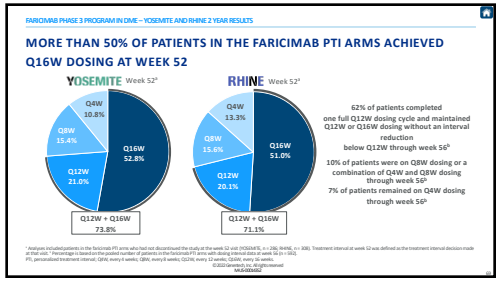


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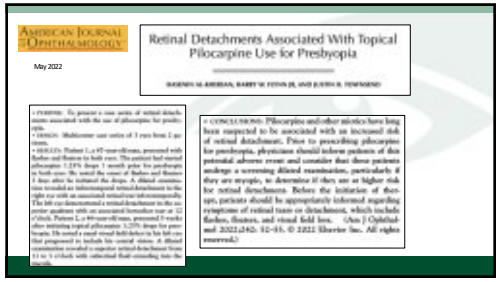
## Vuity to Treat Presbyopia

- 1.25% pilocarpine
- FDA approval Oct 2021
- Positive phase 2 phase 3 results, GEMINI 1 and GEMINI 2
  - 750 patients who used Vuity daily for 30 days
  - **29% of patients experienced a ≥3 line increase** in distance-corrected near visual acuity at day 30, hour 3 vs 10% in controls.
  - Adverse events (AE) were all mild and included headaches (14.1%), visual impairment (4.3%), conjunctival hyperemia (2.5%), vision blur (2.5%), eye irritation (2.5%), eye pain (2.5%), increased lacrimation (2.5%), nausea (2.5%), and punctate keratitis (0.6%)
  - **no cases of retinal tears, RD, macular holes, or vitreomacular traction**

74

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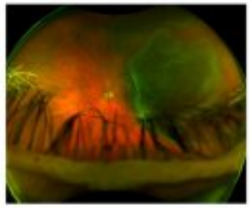

Herein, we present cases of retinal detachment from 3 eyes of 2 patients occurring after the initiation of pilocarpine 1.25% topical ophthalmic drops for presbyopia. Although these cases of retinal detachment cannot be definitively associated with the initiation of the pilocarpine therapy, the incidence shortly after initiation of treatment is concerning. Particularly, the occurrence of a bilateral concurrent retinal detachment in the patient in case 1 who became symptomatic with flashes and floaters just 3 days after starting the pilocarpine 1.25% topical drops warrants further investigation of retinal detachments as a possible adverse effect of treatment.

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65 yo Optometrist
- Small scotoma in 1 eye 10 min after instillation of Vuity
- Does her own OCT and has VMT
  - Fellow eye: PVD and multiple retinal tears

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## Retinal Complications Associated with Vuity

- FDA Adverse Events Reporting System (FAERS) Dashboard
  - 433 Total Cases
  - 86 viewed as Serious Cases
    - 28 retinal detachments
    - 18 retinal tears
    - Vitreomacular traction
    - Visual field defect

Sept 30, 2022

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## Why Retinal Complications?

- Contraction of the ciliary body
- Rapid anterior displacement of the vitreous
  - Shifting the vitreous body forward
- Resulting in traction on the retina
- May predispose some patients
  - Lattice degeneration and peripheral retinal pathology
  - Abnormal vitreomacular interface

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## The Optometrist's Role in Diagnosing and Managing Patients with Diabetes

- Optometrists play a critical role as a part of the healthcare team managing patients with diabetes
- It is paramount to recognize the presence of diabetic retinopathy
- Recognizing when it's more than moderate nonproliferative diabetic retinopathy
- Accurate DR staging is critical for timely referral and treatment
  - Clinical exam vs. wide-field imaging

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2022 National Diabetes Statistics Report

## Diabetes is Occurring in Epidemic Proportions

- Affects over 11% of the US population (37.3 million people)[1]
  - **14% of all US adults ≥18 years old**
- By 2050 between 1 in 5 and 1 in 3 US adults (estimated) will have diabetes


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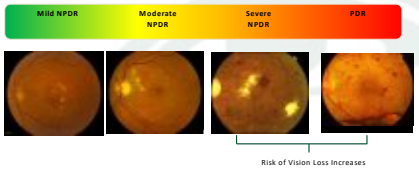
## Diabetic Retinopathy Severity Scale

International Scale

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## ETDRS vs. International Classification of DR

| Diabetic Retinopathy | ETDRS | International Scale |
|---|---|---|
| Mild NPDR | At least one Ma | Ma only |
| Moderate NPDR | H/Ma ≥ standard Slide 2A or soft exudates, VB, IRMA | More than just Ma, but less than Severe NPDR |
| Severe NPDR | One of the following:<br>• H/Ma ≥ standard photo 2A in all 4 quadrants<br>• VB present in at least 2 quadrants<br>• IRMA > standard photo 8A in at least 1 quadrant | No signs of PDR with any of the following:<br>• > 20 intraretinal hemorrhages in each of 4 quadrants;<br>• Definite VB in ≥2 quadrants;<br>• Prominent IRMA in ≥1 quadrant |
| PDR/High Risk PDR | | Severe NPDR and one or both of the following:<br>• Neovascularization;<br>• Vitreous/preretinal hemorrhage |

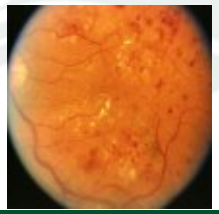
Early Treatment Diabetic Retinopathy Study Research Group. Early Treatment Diabetic Retinopathy Study design and baseline patient characteristics. ETDRS report number 7. Ophthalmology. 1991;98:741.

84

## Severe Nonproliferative Diabetic Retinopathy (NPDR)

**4-2-1 Rule**

- 20 Hemorrhages & Ma in each 4 quadrants
- Significant venous beading in 2 quadrants
- Prominent IRMA in 1 quadrant



85

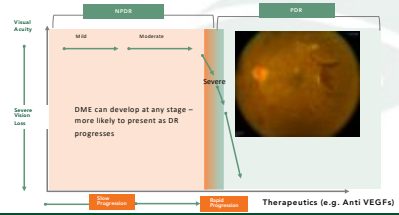
## Risk for Progression to PDR

| | 1 year | 5 year High-Risk PDR |
|---|---|---|
| Mild NPDR | 5% | 15% |
| Moderate NPDR | 12% | 33% |
| Severe NPDR | 52% | 60-75% |
| Very Severe NPDR | 72% | 75% |

https://aao.aberflip.com/i/1183826-evidence-based-clinical-practice-guideline-eye-care-of-the-patient-with-diabetes-mellitus-second-edition/597mk

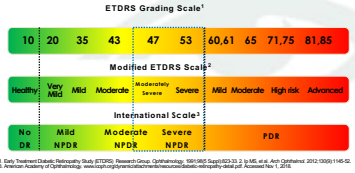
86

## Vision Loss in Diabetic Retinopathy




87

## History of DR Severity Scales – ETDRS, Modified ETDRS, and International




1. Early Treatment Diabetic Retinopathy Study (ETDRS) Research Group. Ophthalmology. 1991;98(5 Suppl):823-33. 2. Ip MS, et al. Arch Ophthalmol. 2012;130(9):1145-52. 3. American Academy of Ophthalmology. www.aopho.org/sites/default/files/resources/diabetic-retinopathy-table2.pdf. Accessed Nov 1, 2018.

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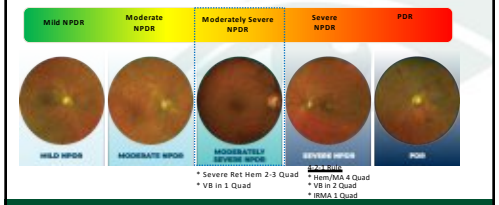
## Diabetic Retinopathy Severity Scale

International Scale




* Severe Ret Hem 2-3 Quad
* VB in 1 Quad

* Hem/MA 4 Quad
* VB in 2 Quad
* IRMA 1 Quad

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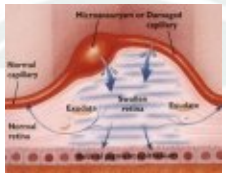
## Macular Edema

- Thickening of the retina
- Secondary to leaky microaneurysms
- **90% of visual loss in diabetes**

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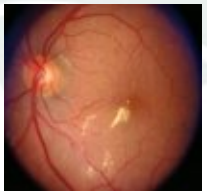
## CSME

- Retinal thickening within 500 microns from the center of the FAZ
- Hard exudates associated with retinal thickening 500 microns from center of FAZ
- Zones of retinal thickening > 1 DD in area, any part of which is 1 DD from the center of the fovea



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## Diabetic Macular Edema (DME)

- CSME
- Center involved vs. Not center involved

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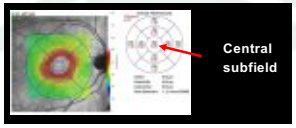
## 2017 DME Classification:

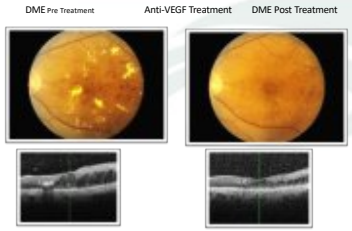
**Center Involved of Not?**

- ETDRS definition of "clinically significant macular edema" modified in era of OCT
- Randomized clinical trials of anti-VEGF agents used presence of DME in **OCT central subfield**




Nguyen, Quan Dong, et al. "Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE." Ophthalmology 116.6 (2009): 2175-2181.e1.
Brown, David M., et al. "Intravitreal aflibercept for diabetic macular edema: 100-week results from the VISTA and VIVID studies." Ophthalmology 122.10 (2015): 2044-2052.

93

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## The Debate…

- Is it better to treating early – before they develop PDR?
  - Would earlier treatment result in better visual outcomes?
  - Would it result in less # of injections?
  - Does the cost/burden of treatment warrant early treatment?

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"The Fate of 47…"

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## PANORAMA

- Phase 3 double-masked, randomized **Prospective Study**
- Efficacy and safety of intravitreal **aflibercept** (IAI) in patients with **moderately severe to severe NPDR**
  - DRSS 47 & 53
- Primary Endpoint:
  - Week 24
  - Proportion of patients improving ≥2 steps on DRSS
  - IAI groups combined
- Follow up through week 100

Wykoff, CC. Keypoints from the Phase 3 PANORAMA Study. (July 2018) American Society of Retina Specialists, Annual Meeting, Vancouver, BC, CA.

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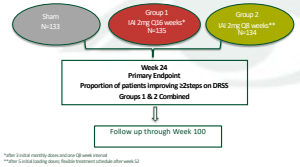
## Phase 3 Double-masked, Randomized Prospective Study Efficacy and Safety of Intravitreal Aflibercept (IAI) in Patients with Moderately Severe to Severe NPDR (DRSS Level 47 and 53) N=402




Wykoff, CC. Key points from the Phase 3 PANORAMA Study. (July 2018) American Society of Retina Specialists, Annual Meeting, Vancouver, BC, CA.

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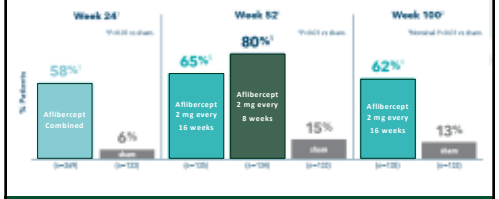
## Patients achieving a > 2 step improvement in ETDRS-DRSS Score at 52 and 100 Week

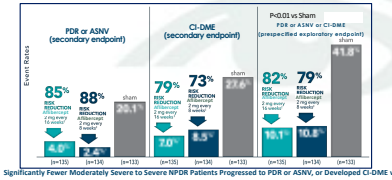



Wykoff CC. Intravitreal Aflibercept for Moderately Severe to Severe Non-Proliferative Diabetic Retinopathy (NPDR): 2 Year Outcomes of the Phase 3 PANORAMA Study. Data presented at: Angiogenesis, Exudation and Degeneration Annual Meeting; February 8, 2020; Miami, FL.

99

## Prevent the Development of PDR, ASNV, or CI-DME

Progression to PDR or ASNV or Development of CI-DME Through Week 52




Significantly Fewer Moderately Severe to Severe NPDR Patients Progressed to PDR or ASNV, or Developed CI-DME vs Sham Through Week 52 in the PANORAMA Study

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## Prevent the Development of PDR, ASNV, or CI-DME

Week 100


Wykoff CC. Intravitreal Aflibercept for Moderately Severe to Severe Non-Proliferative Diabetic Retinopathy (NPDR): 2 Year Outcomes of the Phase 3 PANORAMA Study. Data presented at: Angiogenesis, Exudation and Degeneration Annual Meeting; February 8, 2020; Miami, FL.

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## Diabetic Retinopathy Severity Score (DRSS)

| Level* | ETDRS DRSS Severity | Description |
|---|---|---|
| 1 | 10 and 12 | DR absent |
| 2 | 14, 15, 20 | DR questionable, microaneurysms only |
| 3 | 35 | Mild NPDR |
| 4 | 43 | Moderate NPDR |
| 5 | 47 | Moderately severe NPDR |
| 6 | 53 | Severe NPDR |
| 7 | 60, 61 | Mild PDR |
| 8 | 65 | Moderate PDR |
| 9 | 71 | High-risk PDR |
| 10 | 75 | High-risk PDR |

2-step improvement in DRSS
From DRSS level 53, Severe NPDR (level6)
To DRSS level 63, Moderate NPDR (level 4)

The Diabetes Control and Complications Trial. *Arch Ophthalmol.* 1995;113:36-51; Aiello LM. *Am J Ophthalmol.* 2003;136:122-135

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PANORAMA
Week 52 Results

- Vision threatening complications were reduced by 82% to 85% compared with sham injection
- Development of CI-DME was reduced by 68% to 74% compared with sham

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Ophthalmology Retina October 2018

**Ranibizumab Induces Regression of Diabetic Retinopathy in Most Patients at High Risk of Progression to Proliferative Diabetic Retinopathy**

- The main objective of this exploratory post hoc analysis of the RIDE and RISE clinical trials was to examine DR outcomes in patients who were at highest risk for progressing to PDR (baseline DRSS levels 47/53).

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**RISE AND RIDE POST HOC ANALYSIS**
PATIENTS WHO HAD NPDR AND PDR WITH DME

CENTIS DIABETIC MACULAR EDEMA

**Post hoc analysis:**

- Included 746 patients (LUCENTIS 0.3 mg, n=245; LUCENTIS 0.5 mg, n=247; sham, n=254) who had DR with DME and were randomized for treatment in RISE & RIDE
- DR outcomes with LUCENTIS were evaluated in patients along the spectrum of the severity scale (baseline ETDRS levels 10–75)
- Patients with prior panretinal photocoagulation (PRP) were not included in this analysis

Wykoff et al. *Ophthalmology Retina*. 2018.

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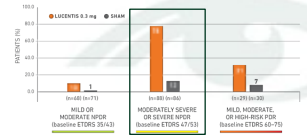
**RISE AND RIDE POST HOC ANALYSIS**
≥2-STEP REGRESSION IN DR AT 2 YEARS

CENTIS DIABETIC MACULAR EDEMA




**Limitations** of this analysis include that it is post hoc (ie, not prespecified in protocols). The statistical significance of these results cannot be determined, and the clinical significance of these results is unknown. Results between groups should not be compared.

Wykoff et al. *Ophthalmology Retina*. 2018.

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Ranibizumab induces Regression of Diabetic Retinopathy

Wycoff et al, Ophthalmology Retina October 2018

- At month 24, DR levels 47/53 **80% of eyes had a 2-step** improvement in ranibizumab treated eyes vs 12% in the sham treated eyes
- The regression of DR was not seen in earlier in less severe DR or in more severe DR
- **Study Conclusion**: In patients with baseline DR levels 47/53, ranibizumab treatment reduced the probability of patients experiencing a new proliferative event at month 36 by **3 times vs. sham treatment**

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JAMA Ophthalmology | Original Investigation

**Effect of Intravitreous Anti-Vascular Endothelial Growth Factor vs Sham Treatment for Prevention of Vision-Threatening Complications of Diabetic Retinopathy**
The Protocol W Randomized Clinical Trial

CONCLUSIONS AND RELEVANCE: In this randomized clinical trial, among eyes with moderate to severe NPDR, the proportion of eyes that developed PDR or vision-reducing CI-DME was lower with periodic aflibercept compared with sham treatment. However, through 2 years, preventive treatment did not confer visual acuity benefit compared with observation plus treatment with aflibercept only after development of PDR or vision-reducing CI-DME. The 4-year results will be important to assess longer-term visual acuity outcomes.

Jama Ophthalmology, March 30, 2021

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PROTOCOL W: EYLEA VS. SHAM IN MODERATE TO SEVERE NPDR (DRSS OF 43 – 53)

PROTOCOL W Study Design

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## Protocol W: 2 Year Conclusions


- The 2-year data did not confer visual acuity benefit compared to sham group
  - Note: sham group received aflibercept once they developed DME or PDR

Jama Ophthalmology, March 30, 2021

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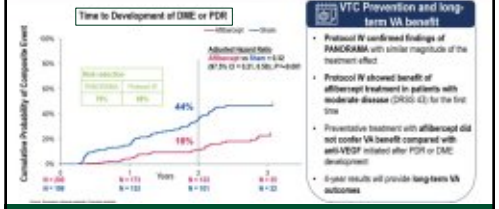
## Protocol W: 2 Year Conclusions




Jama Ophthalmology, March 30, 2021

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## Is there a benefit from early Tx of Severe NPDR?

- So, what is the benefit of early treatment if it doesn't result in any visual acuity improvement?
- Does it matter that there is a regression in DR if when all and said and done the patient ends up with the same visual outcome?

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Artificial Intelligence

113

## AI device for detecting diabetic retinopathy earns swift FDA approval

- Images captured by Topcon NW400 non-mydriatic retinal camera
- Images sent to a cloud-based server that utilizes the IDx-DR software and a 'deep learning' algorithm
- The technology was **87% sensitive and 90% specific** for detecting **more than mild** diabetic retinopathy
- The algorithm correctly identified **100% of with ETDRS level 43 or higher (moderate NPDR)**

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August 6, 2020 FDA Clears EyeArt:
AI System for Diabetic Retinopathy Detection

EyeArt is the first FDA cleared AI technology for autonomous detection of both more than mild and vision-threatening diabetic retinopathy. It is the most extensively validated autonomous AI technology, tested in the real-world on more than half million patients and nearly two million retinal images globally.

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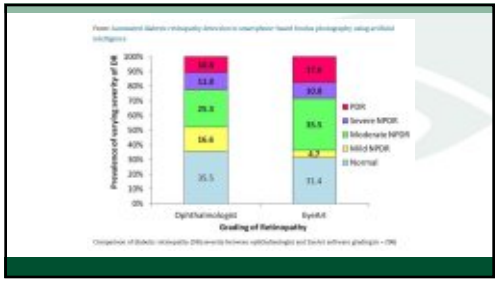


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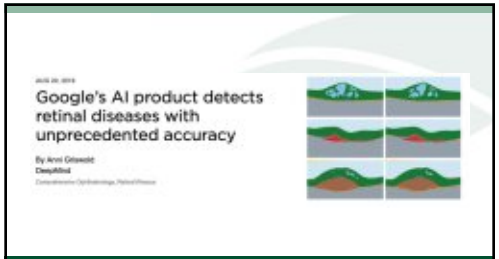


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Thailand Study

- Many of the images rejected (20%)
  - Poor lighting
- Images uploaded to the cloud but issues with internet speed
- Time wasted re-taking images
- **When it did work – it worked well**
  - **One nurse was able to see > 1000 pts**
- Patients didn't really care that it was an AI rather than a human reading their images – just wanted good experience

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Google Health wants to speed up healthcare with machine learning and smartphones

Accurate results in a flash

121

May/June 2022 | Features

RT | Retina Today

Artificial Intelligence in AMD Imaging

Here is a look at what to expect as this tool becomes more ubiquitous in research and the clinic.

AT A GLANCE

- Advances in retinal imaging have led to the identification of biomarkers for AMD progression that may one day shape how we diagnose, treat, and follow patients with AMD.
- Artificial intelligence (AI) algorithms may be able to provide analyses to assist physicians in diagnosing conditions based on specific features extrapolated from large volumes of imaging data.
- Researchers have demonstrated AI's ability to objectively identify, localize, and quantify subretinal fluid and high-risk structural biomarkers on OCT using a fully automated tool.
- AI-based imaging may be particularly useful in the era of personalized medicine, where we may be able to accurately predict outcomes and choose the optimal therapeutic strategies.

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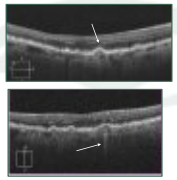
## OCT Biomarkers May Help Predict Conversion to GA or Wet AMD

- Drusen Volume
- Hyper-Reflective Foci (HRF)
- Retucular pseudo drusen
- Incomplete Retinal Pigment Epithelial and Outer Retinal Atrophy (iRORA)
  - Without RPE loss
  - Replaces "Nasacent GA"
- Hyper-transmission defects
- OCT-Reflective Drusen Substructures



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## OCT Biomarkers May Help Predict Conversion to GA or Wet AMD

Review Article

OCT Biomarkers in Neovascular Age-Related Macular Degeneration: A Narrative Review

Retinal Progression Biomarkers of Early and Intermediate Age-Related Macular Degeneration

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## What do we tell our patients who have genetic link to AMD?

53 yo white male

- Father lost central vision from AMD by age 70
- RE macular is normal; LE has a few small drusen

- What do you tell this patient?
  - Genetic testing
  - Nutritional supplement

125

## Gene Therapy: Are We On the Verge of A Gene Therapy Explosion?

126

## Gene Therapy for Inherited Retinal Disease

- Gene therapy refers to the use of genetic material (DNA or RNA) **"implanted"** to modify gene expression, in order to treat disease
- Delivering a working copy to a damaged gene that causes the disease
  - The goal is **restoration of gene function** in the case where a mutation has inactivated it
- **Inactivate a mutated gene** that is not functioning correctly
  - Autosomal dominant RP (adRP) caused by mutations in the rhodopsin (*RHO*) gene

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## CRISPR and CRISPR-CAS Proteins

- CRISPR is a sequence information
- Cut and manipulate our genomic material
- Replace DNA in the area of interest


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## The Eye is the Ideal Environment Gene Therapy

- Monogenic nature of most Inherited Retinal Diseases (IRD)
- Retina is a favorable favorable target for administering genetic vectors
- Immunoprivileged environment
- Direct visibility
- Multiple ways to assess sensitivity and function

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## Inherited/Hereditary Retinal Disease (IRD)

- A group of genetically heterogeneous disorders that result in a myriad of clinical presentations and can cause varying levels of vision loss including total blindness
- Over **100 IRD disease entities** and are caused by various **defects in over 300 genes.**
- They are generally untreatable
- **Retinal dystrophies can broadly be divided into two forms:**
  - Monogenic (single-gene): Leber's (LCA), Stargardt's, Choroideremia
  - Complex (multifactorial) diseases: RP

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## Gene editing (genome surgery)

- An endonuclease enzyme (bacterial in origin) is guided to specific target DNA sequence by a pre-designed RNA sequence
- DNA repair mechanisms then modify the gene
  - Correct a mutation
  - Introduce a new sequence
  - Modulate its transcription
- Offers a solution for targeting a **faulty gene** so it can be **suppressed** to restore normal function

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## How to you access or even get to the specific gene in order to alter/change its function?

"Cell Specific Promotor"

- Access/target the gene via the use of a vector – often viral
  - Attach the gene editing tool to a virus and then inject it into the eye
- Infects the target cell to deliver a therapeutic gene
- Which vector used depends on the which cells are targeted and the size of the gene we wish to modify


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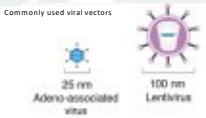
## Gene Therapy for Treating Retinal Disease

- Retinal gene therapy involves a **subretinal** or **intravitreal** injection of a viral vector,
- Viral vector infects target cells to deliver a therapeutic gene, or transgene

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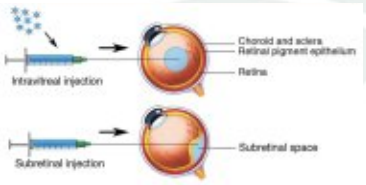
## Delivery of the Vector

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**FDA approves novel gene therapy to treat patients with a rare form of inherited vision loss**

135

**Genome Editing and Gene Therapy to Treat Angiogenesis**
**New developments have the potential to change the way retina specialists treat disease.**

- **Luxturna** (voretigene neparvorec-rzyl; Spark Therapeutics) became the 1st in vivo gene therapy approved by the US Food and Drug Administration, in 2017
- This historic landmark demonstrated that gene therapy is not only safe and effective, but also that it is potentially the answer to a number of medical conditions
- This new frontier of **precision medicine** aims to target disease more directly
- May result in a one-time treatment delivering genes that express therapeutic factors for months or years

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## Leber's Congenital Amaurosis (LCA)

- **Monogenetic inherited retinal disease** (IRDs) that develops as a result of a mutation in the RPE65 gene (Biallelic mutation)
- **RPE65 gene** provides instructions for **making an enzyme** that is essential for normal vision
- Mutations in the RPE65 gene lead to **reduced or absent levels of RPE65 activity**, blocking the visual cycle and resulting in impaired vision
- Results in progressive deterioration of vision over time
  - Begins in childhood or adolescence
  - Ultimately progresses to complete blindness

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## Gene Therapy for LCA

- Luxturna works by delivering a normal copy of the RPE65 gene directly to retinal cells
- These **retinal cells then produce the normal protein** that converts light to an electrical signal in the retina to restore patient's vision loss
- Luxturna uses a naturally occurring adeno-associated virus, which has been modified using recombinant DNA techniques, as the vehicle to deliver the normal human RPE65 gene to the retinal cells to restore vision

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## Biallelic RPE 65 Mutation

- 41 patients between the ages of 4 and 44 years enrolled
- All participants had confirmed biallelic RPE65 mutations
- The primary endpoint: **Ability to navigate an obstacle course at various light levels**
  - The group of patients that received Luxturna demonstrated significant improvements in their ability to complete the obstacle course at low light levels as compared to the control group

Cost: ~ $425,000 per eye

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## How Effective is Luxturna?

- Effectiveness was measured by people's improvement in navigating an obstacle course at different light levels
- Treatment affect as early as 30 days
- **At 1 year, 65% of people who received Luxturna passed the obstacle course at the lowest light levels**
  - **No pts prior to treatment were able to navigate the obstacle course**

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## Gene Therapy for Other Hereditary Retinal Diseases

**Applied Genetic Technologies Corporation (AGTC)**

- Biotechnology company developing gene therapies for retinal degenerative diseases and other conditions
- Positive results in gene therapy for X-linked RP (RPGR mutation) and achromatopsia (CNGB3 and CNGA3 mutations)
- **Stargardt disease:** dual-vector AAV technology, which delivers the ABCA4 gene in two halves
  - When the halves are delivered to the recipient's photoreceptors, they recombine to produce a whole, fully functional ABCA4 gene

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## Gene Therapy for Other Hereditary Retinal Diseases

**Allergan**

- Using viral vectors to deliver CRISPR-Cas9 to genetically treat **Leber congenital amaurosis**.
  - The is a very precise gene editing technique
- BRILLIANCE study (Allergan; Editas Medicine) Phase 1/2, a CRISPR-Cas-based genome editing treatment for the treatment of Leber congenital amaurosis type 10
  - 18 participants will be enrolled in up to 5 cohorts to evaluate up to 3 dose levels of AGN-151587 in this study
  - This is the first time this technology has been used for gene therapy in the eye.
  - The medication is administered via a subretinal injection

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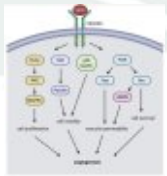
## Targeting Angiogenesis at a Genetic Level

- CRISPR and Cas protein gene editing
- Permanently disrupt or reduce the production of pathologic factors
- **CRISPR-Cas treatment can potentially be delivered by directly manipulating the genetic code**



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## Gene therapy for AMD

- Complex multifactorial disease
- Both Environmental and genetic factors contribute
  - Smoking
  - Oxidative stress
- The immune system plays an important role in AMD
  - CFH is a key driver as well as other complement genes
- Other genes involved in Oxidative metabolism and Lipid Metabolism

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## Gene Therapy in Eye Care

- 2 companies are using **adenoviral vectors (AAV)** to deliver genes that makes cells produce either a **ranibizumab-like protein** or an **aflibercept-like protein**
  - Reduce/Stop the need to anti-VEGF injections
- Numerous companies are using this same technique to target monogenetic inherited retinal degenerations

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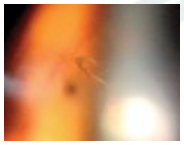
## Floaterectomy?

- Is it too dangerous or a reasonable option?

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## The Burdon of Floaters

**Retrospective Study Bascom Palmer Eye Institute 2008-2011**

- 7.2% of patients referred to a retinal specialist had floaters
- 5th most common diagnosis over that time
  - > 60 yo 3rd most common Dx
- Vitrectomy: very successful, technically simple, with low side-effect profile
  - Risk of Cataract, ERM, and retinal tears/detachments

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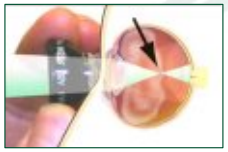
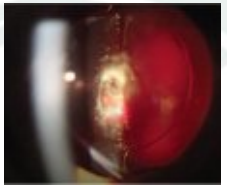
## Options for Treatment of Floaters

- Yag vitreoloysis
- Pars plana vitrectomy

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## Important Considerations in Patients with Floaters

Are they acute or chronic?

- Acute Floaters – often from PVD
  - Usually resolve
- Chronic floaters that impact daily activities

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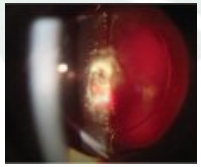
## Reasons for Surgery for Floaters

Symptoms that impact the quality of life

- Unable to read continuously
- Unable to safely drive a car
  - The floaters/cloud moves in front of their vision and they nearly have to pull over for fear of having an accident
- Affects ability to perform your job



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## The Ideal Candidate for Treatment of Floaters

- Symptomatic
- Pseudophakic
- PVD

## The NOT Ideal Candidate for Treatment of Floaters

- Young
- Phakic
- Attached vitreous
- High myope

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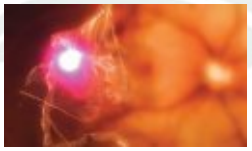
## Laser Vitreolysis for Floaters

- Done with a Yag
- Highly variable results
- Complications:
  - Cataract (hitting the lens)
  - Posterior capsule tears
  - Retinal burns
  - Foveal burns
  - Choroidal rupture
  - Choroidal hemorrhages
  - Retinal tear



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**Long-Term Follow-Up of Efficacy and Safety of YAG Vitreolysis for Symptomatic Weiss Ring Floaters**

- 35 of 52 patients randomized to Yag vitreolysis or Control followed for 2.3 years
- 50% felt their symptoms were significantly or completely better at 6 months
  - ~60% overall improvement in symptoms
- 3 patients developed retinal tears after 6 months (not symptomatic)

Ophthalmic Surg Lasers Imaging Retina 2020

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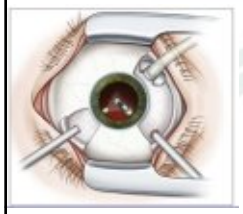

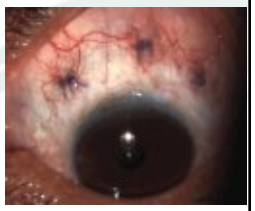

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## Vitrectomy 2023

- Smaller-gauge instruments (25 or 27) compared with the 20-gauge needles used less than 15 years ag
- Smaller vitrectomy instruments allow for sutureless procedures
  - Smaller sclerotomy
  - Trocars allow for small, thin-wall cannula
- Less inflammation
- Fewer complications
- Much greater success rate

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## Risk Factors for Vitrectomy

- Cataract
- Retinal tear or detachment
- ERM/Macular pucker
- Macular edema
- Endophthalmitis

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## Induce a PVD….or not

- Risk of developing a retinal tear by inducing PVD
- Reduced risk/time of developing cataract with partial vitrectomy

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## Long-term Safety of Vitrectomy for Patients with Floaters

- 66 eyes in 52 patients (age = 63 ± 12 years) were included
- 36/66 (54.5%) eyes were phakic
- Average duration of coping was 30 months
- Etiology of floaters was PVD in 44/66 (67%), myopia in 19/66 (28%), asteroid hyalosis in 8/66 (12%)
- Retinopexy for retinal breaks occurring at the time of PVD was performed in 16 eyes (36% of all eyes with PVD; 24% of all eyes), a minimum of 3 months prior to vitrectomy
- 22 eyes without PVD: PVD NOT induced and vitreous remained intact peripherally
- Main outcome: incidence of ret tears/detachments and cataract requiring surgery

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## Long-term Safety of Vitrectomy for Patients with Floaters

- Floater symptoms resolved in 65 of 66 eyes (98.5%)
- No patients (0/66; 0%) developed retinal breaks, hemorrhage, infection, or glaucoma (3 month – 3 years)
- No retinal breaks/ detachments in the 22 patients without PVD pre-operatively (0/22 vs 9/30)
- Only 7/36 (19%) phakic eyes developed cataracts requiring surgery, an average of 16.5 months post-vitrectomy (7/36 vs 18/36 (50%)

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2018

## Long-Term Safety and Efficacy of Limited Vitrectomy for Vision Degrading Vitreopathy Resulting from Vitreous Floaters

**Methods** 195 Eyes

Limited vitrectomy with 25-gauge instruments was performed without surgical PVD induction, preserving 3 to 4 mm of retrolental vitreous in phakic eyes. Follow-up averaged 32.6 ± 23.5 months (range, 3–115 months), with 2 years or more in 144 eyes, 3 years or more in 88 eyes, 4 years or more in 51 eyes, and 5 years or more in 24 eyes.

**Conclusions**

Limited vitrectomy for Vision Degrading Vitreopathy decreases vitreous echodensity, improves patient well-being, improves VA, and normalizes CSF. The long-term efficacy and safety profiles suggest this may be a safe and effective treatment for clinically significant vitreous floaters, warranting a prospective randomized trial.

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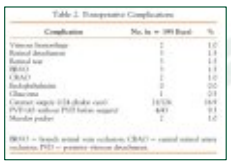

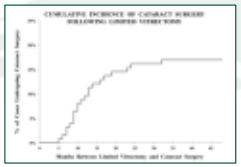

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Would you Recommend Surgical Intervention for patients with intractable Symptoms of floaters?

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## Hot Topics in Retina: Summary

- Exciting time for innovative treatments for retinal disease
- Paradigm shift in the management of diabetic retinopathy
  - Earlier treatments
  - Earlier referrals
- New Treatments for Wet AMD that may reduce the burdon to treatments for patients
  - Emerging treatments in the pipeline for dry AMD
- We are witnessing the dawn of a new age in using genetics to treat eye disease
- Imaging continues to get better and better and important part of clinical practice

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