# UPDATE ON AMD 2022

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## Disclosures

- Speakers bureau and/or Advisory Board for:
  - Genentech
  - I care
  - LKC Technologies
  - MacuLogix
  - Notal Vision
  - Novartis
  - Optovue
  - Regeneron
  - Science Based Health
  - Visible Genomics

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## Introduction

- AMD is the leading cause of vision loss *in Americans* over the age of 60
- Advanced AMD is the leading cause of vision loss and irreversible blindness *worldwide* in those over the age of 50
- As many as 11 million Americans have some level of AMD
  - Expected to increase to nearly 22 million by 2050
- More than glaucoma (2.2 million) and DR (7.7 million) COMBINED

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## Introduction

- **Exciting time to be interested in AMD**
- **Many new treatments now available for AMD**
  - **Years ago, we had nothing at all to offer patients with AMD**
- **Current Treatments**
- **Potential Treatments**
- **New Diagnostic Equipment**

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## Dry AMD

- **Currently mainstay treatment for Dry AMD revolves around prevention of progression through vitamins, nutrition and lifestyle changes**
  - **Rheophoresis, Laser, Anecortave Acetate did not prove effective**
  - **Smoking #1 modifiable risk factor for getting AMD as well as its progression!**
    - **One study showed 90% of pts with AMD were not advised to quit smoking**
- **Early detection of conversion from dry to wet may result in better treatment for patients**

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## "Wet" AMD

- Neovascular "wet" AMD
  - Mainstay of treatment consists of serial intravitreal injection of anti-VEGF agents

| Anti-VEGF Agents | Pegaptanib (Macugen®) | Ranibizumab (Lucentis®) | Aflibercept (Eylea®) | Brolucizumab (Beovu®) | Bevacizumab (Avastin®) |
|---|---|---|---|---|---|
| **FDA approval** | 2004 | 2006 | 2011 | 2019 | Not approved |
| **Pivotal studies** | VISION | ANCHOR<br>MARINA<br>IVAN | VIEW<br>1 and 2 | HAWK HARRIER | CATT |

  - VEGF inhibitors have demonstrated *improved visual and anatomic outcomes* compared with other therapies

VEGF = vascular endothelial growth factor.

AAO. AMD preferred practice guidelines, 2019 (www.aao.org/preferred-practice-pattern/age-related-macular-degeneration-ppp). Kulkarni K, Prenner JL. *Rev Ophthalmol.* 1/15/2006. (www.reviewofophthalmology.com/article/an-update-on-macugen-trials). URLs accessed 4/30/2020.

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## Anti-VEGF Agents

- VEGF is a primary driver of blood vessel growth and leakage in AMD
- Anti-VEGF agents block and neutralize VEGF
  - Results in decreased intra- and sub-retinal fluid
  - May also decrease risk of scar tissue formation
- Serious adverse effects (endophthalmitis) rare
- Less serious events (subconjunctival hemorrhage, vitreous hemorrhage, floaters) are also uncommon

Pongsachareonnont P, et al. *Clin Ophthalmol.* 2018;12:1877-1886. Yeo NJY, et al. *Front Pharmacol.* 2019;10:1363. Holz FG, et al. *Br J Ophthalmol.* 2016;100:1623-1628. American Society of Retina Specialists (ASRS). Intravitreal injections. (www.asrs.org/content/documents/fact-sheet-30-intravitreal-injections.pdf). Sukgen EA, et al. *Int Ophthalmol.* 2017;37:215-219. Living well with low vision. (https://lowvision.preventblindness.org/2013/06/25/betadine-and-eye-pain/). URLs accessed 5/30/2020.

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## Anti-VEGF Agents: Outcomes

| Lucentis[1] | Eylea[2,3] | Beovu[4] |
|---|---|---|
| • **94% stable vision at 2 years** | • 95% of patients treated maintained acuity | • ~30% gained at least 15 letters by year 1 |
| • **34–41% gained 15 letters or more** | • 7.9–10.9 letters mean improvement of vision | • Less fluid and greater reduction in CST vs aflibercept |
| • **Average gain of 11.3 letters at 1 year and 10.7 letters at 2 years** | | • At 1 year, half of subjects on 3-month dosing |

**1. Brown DM, et al. *Ophthalmology.* 2009;116:57-65.e5. 2.Nguyen QD, et al. *Invest Ophthalmol Vis Sci.* 2011;52: abstract 3073. 3. Schmidt-Erfurth U, et al. *Invest Ophthalmol Vis Sci.* 2011;52:E-Abstract 1650. 4.Dugel PU, et al. *Ophthalmology.* 2020;127:72-84.**

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## Anti-VEGF Agents: Delivery and Dosage

- Delivered intravitreally
- Dosing schedule and agent used varies
- In general
  - Loading dose with 1 injection per month for 3 months, then inject based on FA, OCT, or other clinical findings
  - Reduces patient burden while still delivering good results
- Serious adverse effects (endophthalmitis) rare
- Less serious events (subconjunctival hemorrhage, vitreous hemorrhage, floaters) are also uncommon

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## Beovu ( brolucizumab)

- Novartis
- FDA approved Oct 9, 2019
- Greater fluid resolution than previous agents with similar vision gains on 3 mos dosing
- Based on Hawk and Harrier Phase 3 trials

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## Beovu ( brolucizumab)

- Hawk and Harrier Study: compared to Eylea
  - 30% of pts gained at least 15 letters by year 1
  - Greater reduction in central retinal thickness at week 16 and 1 year than Eylea
  - Fewer pts with subretinal fluid than Eylea
  - Real key is extended dosing
    - After 3 monthly loading doses
      - By year 1, > ½ pts on 3 mos dosing
      - Rest were 2 mos dosing
  - Safety profile similar to Eylea

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## Beovu update

- In Feb, 2020, American Society of Retinal Specialists (ASRS) issued a warning reporting 14 cases of retinal vasculitis following injection of Beovu
  - 11/14 were occlusive and resulted in vision loss
- In March, Novartis concluded that retinal vasculitis, retinal artery occlusion, or severe vision loss occurred in 8.75-10.08 out of 10,000 injection
- Added to warning label
  - Intraocular inflammation in 4% of pts
  - Artery occlusion in 1%
- Advised to avoid if pts had h/o inflammation to any other anti-Vegf agent

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## Faricimab

- Roche/Genetech
- First bi-phasic antibody for intraocular use
- One arm: Vegf-A inhibitor
- Other arm: Angiopoietin-2 (Ang-2)inhibitor
  - growth factor that promotes vascular destabilization and and inflammation
- Dual inhibition of VEGF and Ang-2 have proven more effective than inhibiting either target alone

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## Vabysmo™

- Farcimab FDA approved January 3, 2022 for AMD and DME
- AMD: 4 initial monthly doses, then every 2,3 or 4 mos, based on outcome
- DME: 4 initial monthly doses, then every 1-4 mos, based on outcomes
- COMINO and BALATON studies underway to evaluate efficacy and safety in people with macular edema following RVO

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## moVabysom

- Avenue/Stairway
  - Looked at 2 doses ( 6.0 and 1.5 mg) of Faricimab vs Lucentis
  - Good anatomic improvement and vision gains similar to Lucentis
    - Mean vision gains of 9.6 to 11.4, depending on dose and schedule
      - Faricimab 6.0 mg q 16 weeks had greatest gain (11.4)
  - TENAYA/LUCERNE
    - Met primary endpoint: people receiving farcimab q 16 weeks achieved VA outcomes that were non-inferior to Eylea q 8 weeks at 1 year
    - Almost half (45%) were injected q 16 weeks

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## Susvimo

- Previously known as Port Delivery System with 100mg/ml Ranibizumab
- FDA approved 10/21
- Non-inferior to Lucentis q month
  - Only 1.6% needed rescue injection before 6mo refill (>98% no rescue)(4/246)
  - VA and anatomical outcomes equivalent after 72mos vs monthly injection
    - Regardless of presence or absence of subretinal or intraretinal fluid
  - +.2 letters after 40 weeks vs .5 in monthly injections

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## Biosimilar

- Per the FDA:
  A biosimilar is a biological product that is approved based on data showing that it is highly similar to a biological product already approved by the FDA (reference product) and has no clinically meaningful differences in terms of safety, purity and potency (i.e., safety and effectiveness) from the reference product, in addition to meeting other criteria specified by law.
  - FDA has approved 31 biosimilars in total
  - Other biosimilars discount price 15-30%

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## Biosimilar Anti-VEGF agents

- Byooviz (Ranibizumab nuna by Samsung Biopls Co)
- First biosimilar approved in ophthalmology
- Approved based on study with 634 patients 1:1 to Lucentis
  - BCVA at wk 52 was +9.79 letters for the biosimilar & +10.41 for the reference product (–0.62; 95% CI)
  - The LS mean change in central subfield thickness was –139.55 mcm for Byooviz and –124.46 mcm for Lucentis (–15.09; 95% CI, –25.617 to –4.563)
- At least 3 more Ranibizumab and 3 Aflibercept biosimilars in development
  - Outlook Pharmaceuticals: LYTENAVA: bevacizumab-Vikg
    - Hopeful approval late this year

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## Importance of Early Treatment: CNV Lesion Size

- Evidence from many trials is clear: smaller lesions respond better to treatment
- MARINA study[1]: larger CNV lesion size at baseline was associated with greater loss of letters in sham-treatment group and less gain of letters in ranibizumab-treated arms
- ANCHOR study[2]: smaller baseline CNVM lesion size was associated with greater gain of letters in those receiving ranibizumab
- CATT trial[3]: larger area of CNVM at baseline was associated with worse VA at 1 year, less gain in VA at 1 year, and lower proportion of patients gaining ≥3 lines of acuity

1. Boyer DS, et al. *Ophthalmology* 2007;114:246-252. 2. Kaiser PK, et al. *Am J Ophthalmol.* 2007;144:850-857. 3. Ying GS, et al. *Ophthalmology.* 2013;120:122-129.

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## Importance of Early Treatment: 2020 Analysis of IRIS Registry

- Real-world patients with neovascular AMD who underwent anti-VEGF treatment
- Study included 162,902 eyes
- Results
  - Patients who presented with VA of 20/40 or better at diagnosis maintained mean VA of 20/40 or better for 2 years after initiating treatment
  - Those who presented with VA worse than 20/40 never reached 20/40 at 1 or 2 years
- Conclusion: baseline VA at diagnosis of wet AMD predicts long-term VA outcomes

Early diagnosis before VA is adversely affected is a key factor in preserving vision in patients with wet AMD

Ho AC, et al. *Ophthalmic Surg Lasers Imaging Retina.* 2020;51:633-639.

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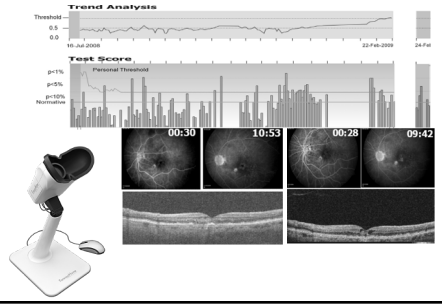
## Foresee Home

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## At-risk Patients May Convert to Wet AMD at Any Point Between Follow-up Visits

Visit **1**

Visit **2**

**Converts after office visit**

**More likely to lose vision**

**Converts between office visits**

**Converts before office visit**

**Less likely to lose vision**

**Reference:** Rauch F, et al. *Retina.* 2012;32(7):1260-1264.

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## AREDS2-HOME Study

| ForeseeHome plus standard care arm | Intent to Treat (ITT) population results | Standard care arm |
|---|---|---|
| 763 participants | 1520 participants | 757 participants |
| 51 CNV events | Mean follow up 1.4 yr ± 0.6 years<br>Mean VA at entry 20/25 | 31 CNV events |
| • Routine monitoring<br>• Patient symptoms<br>• ForeseeHome | | • Routine monitoring<br>• Patient symptoms |

***Primary outcome:** Change in BCVA from baseline to CNV detection*

**Reference:** AREDS2-HOME Study Research Group. *Ophthalmology.* 2014;121(2):535-544.

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## ForeseeHome Arm

Intent to Treat (ITT)

Per Protocol 1 (PP1)

Per Protocol 2 (PP2)

**at least 1 test throughout the study**

**≥ 2x per week (8x per month)**

**Reference:** AREDS2-HOME Study Research Group. *Ophthalmology.* 2014;121(2):535-544.

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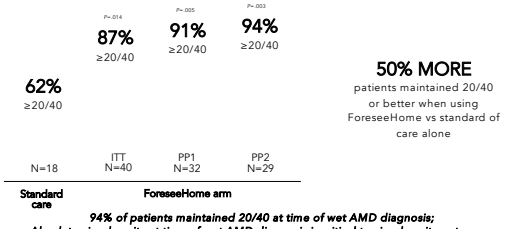
## More patients who used ForeseeHome maintained ≥20/40 VA




***94% of patients maintained 20/40 at time of wet AMD diagnosis; Absolute visual acuity at time of wet AMD diagnosis is critical to visual acuity outcomes at year 1***

**Reference:** AREDS2-HOME Study Research Group. Ophthalmology. 2014;121(2):535-544.

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## Notal Home OCT

- **Notal OCT Analyzer (NOA)**
- **"Uses computer image analysis algorithm to provide automated detection of pathological fluid in exudative retinal disease, including wet AMD, macular edema and retinal vein occlusion"**
- **Performance validated in study comparing sensitivity , specificity and accuracy with 3 retinal specialist**

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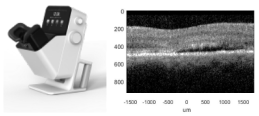
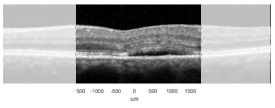
## Patient Self-operated Home OCT provides high quality images

- Patient self-installed and self-operated OCT device
- Monitoring of intra- and subretinal fluid in between office visits
- Provides cross sectional images of the central 10 deg. (3 mm x 3 mm) of the macula in patients with exudative AMD
- 88 B-scans with dense 34 µm spacing ensure high sensitivity of fluid detection
- Test takes approximately 10 sec. per eye
- Device uploads OCT data to cloud

**Home OCT**



**Heidelberg Spectralis (in-office device)**



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## How can I use this information?

- Key is early detection of conversion for DRY to WET AMD
- Evidence from many trials is clear: smaller lesions respond better to treatment
  - CATT trial[3]: larger area of CNVM at baseline was associated with worse VA at 1 year, less gain in VA at 1 year, and lower proportion of patients gaining ≥3 lines of acuity
- IRIS registry: 160K+ pts treated with anti-VEGF
  - Patients who presented with VA of 20/40 or better at diagnosis maintained mean VA of 20/40 or better for 2 years after initiating treatment
  - Those who presented with VA worse than 20/40 never reached 20/40 at 1 or 2 years

Early diagnosis before VA is adversely affected is a key factor in preserving vision in patients with wet AMD

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## OCT Angiography: The Next Chapter in Posterior Imaging

Images retinal microvasculature without dye injection

Displays structure and function from a single imaging system

*2014: OCTA*

*2006: Spectral Domain OCT*

*2002: Time Domain OCT*

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## Fundus Autofluorescence Imaging (FAF)

- Relatively new non-invasive imaging modality developed over past decade
- Has been area of interest in ophthalmic research for over 40 years
- Uses fluorescent properties of lipofuscin
- Aging or disease to photoreceptors causes accumulation of lipofuscin

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## Lipofuscin

- Aging or disease to photoreceptors causes accumulation of lipofuscin
- Lipofuscin is composed of mainly of A2E
- Excessive lipofuscin deposition is considered pathological and associated with visual loss
- Considerable evidence that accumulation of lipofuscin can cause cell death and aptosis

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## AMD/GA

- Described as prognostic marker for GA progression
- Increase AF in the 500um margin around areas of GA may help distinguish between slow and fast progressing lesion
- May be useful moving forward with potential treatment of GA
- Also may help distinguish AMD from mimickers

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## Role of Genetics in AMD

- Risk
- Progression
- Treatment
- Follow up protocol

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## Is AMD in our DNA?

- **AMD is a genetic disease with known markers accounting for at least 70% of the population attributable risk**
- **Other 30% is environmental/lifestyle**
- **Risk factors**
  - **Non-modifiable: age, race, gender**
  - **Modifiable: Smoking, increased BMI, poor diet/nutrition, UV exposure**

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## AMD is a Genetic Disease

| Population Attributable Risk | |
|---|---|
| Condition | Genetics (%) |
| Colorectal Cancer | 35 |
| Diabetes II | 26 |
| Coronary Artery Disease | 40 |
| AMD | 70 |

Those with stronger genetic risk develop more advanced disease earlier in life.

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## Major genetic factors

- CFH
  - Single most important genetic component
  - CFH Y402H
- ARMS2/HTRA1
  - Second most important gene in AMD
- C3
  - Another component of the complement system
- ND2
  - Mitochondrial oxidative phosphorylation molecule
- Others

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## Genetic Factors and Risk: More than additive!

- Former Smokers: 1.29x
- Current Smokers: 2.4X
- Non-Smoker and CFH,Y402H: 7.6X
- Current smoker and CFH,Y420H: 34X

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## AMD Genetic Testing: Arctic DX

Macula Risk NXG

Looks at 15 SNPs as well as smoking, BMI, age and AMD status to determine AMD patients who may progress to advanced AMD and vision loss in

- 2 years
- 5 years
- 10 years

**Cheek Swab**

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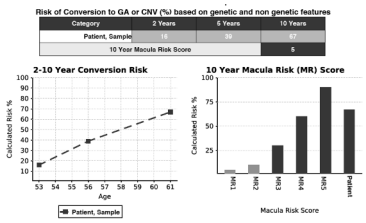
## Patient Report

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## AMD Risk Testing for a Full Spectrum of Patients

**AMD Progression Risk Testing**

For people ≥55yo with or without AMD findings

For people <55yo WITH AMD findings

- Assesses a patient's risk of progression to advanced AMD within 2, 5,10, 20 and 30 years
- Delaying progression to advanced AMD with secondary prevention including AREDS vitamins, increased surveillance (home monitoring)

**Lifetime AMD Risk Testing**

For people <55yo without AMD findings

- Assesses a patient's lifetime risk of developing advanced AMD (GA or CNV) *allowing preventive lifestyle changes at younger age*
- Delaying onset of disease with primary prevention including lifestyle modifications, supplementation (i.e. nutrition) and nutritional intervention



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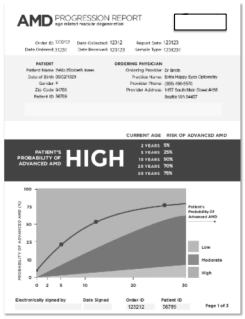


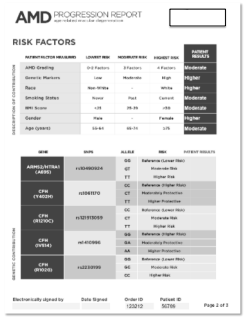


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## How can we use this information?

- Increased surveillance for those at higher risk
  - Sooner/more frequent appointments
  - More diligent home monitoring
- More diligence with modifiable risk factors
- Consider earlier vitamin supplementation
- Potential treatments in the future

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## Potential Therapies

- Currently, there are ≈ 2027 studies evaluating AMD, both Wet and Dry
  - www.clinicaltrials.gov (Sept 2022)
    - More than:
      - glaucoma
      - dry eye
      - diabetic eye disease
- Exciting time to be involved, with many possible therapies that may prove useful for our AMD patients

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## Potential Therapies

- Better Efficacy
  - Better drug
  - Different Mechanism
- Reduced administration
- Different delivery System
  - Eye drops
  - Oral
  - Others

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## Geographic atrophy treatment

- Estimated that 1.2 million Americans suffer from GA
  - > 5 million globally
  - 42% of pts with GA are legally blind
  - Incidence increases with age
  - Responsible for over 20% of all vision loss in pts with AMD
- Treatment geared at decrease in lesion growth
- Various targets being investigated

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## Pegcetocoplan

- Pegcetacoplan (Apellis): synthetic molecule that downregulates C3 and all complement pathways
- Delivered intravitreally
- Phase II Studies: 246 pts
  - At 12 mos, 29% lower rate of GA progression with monthly injections vs sham
  - No difference in visual acuity

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## Pegcetocoplan

- Phase 3 DERBY and OAKS
  - Sept 9, 2021
- OAKS: met primary endpoint
  - 16%-22% reduction in lesion growth at 1 year
- DFERBY: did NOT meet primary endpoint
  - 11%-12% reduction in lesion growth at 1 year
- Will be notified by FDA Nov 26, 2022

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## Zimura

- Avacincaptad pegol, Iveric Bio
- Blocks complement pathway c5a and c5b
- GATHER 1 (Phase II) Study: 286 pts
  - At 12 mos, 27% (2 mg) (4 mg) and 28% (4 mg) less GA growth vs Sham
  - At 18 mos, 28% and 30%
- GATHER 2: Phase III study
  - Released Sept 6, 2022
  - 17.7% reduction in mean rate of growth of GA area over 12 mos
    - 32% reduction in area in US patients

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## Gyroscope therapeutics

- GT005: investigational gene therapy designed to induce expression of CF-I after subretinal delivery
  - CF-I down regulates CF
  - CF related to inflammation and GA lesion progression
- Stage II studies showed well tolerated and had positive effects on lesion size and acuity
- Phase III studies underway
  - Looking for pts with GA and CF-I rare variants (≅3-5%) vs all GA pts
- Bought by Novartis for $800 million up front, plus an additional potential $700 m in incentives

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## If Medical treatment fails…

- Low vision is an important option
  - Traditional and newer / digital devices
    - ORCAM
    - Eyedaptic
  - Surgical options on the horizon
    - ARGUS2 retinal implant
  - Associations and support groups
    - Macularhope.org
    - Sightmatters.com

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