Updates in the management of macular degeneration

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Agenda

1. Types of ARMD
2. Risk factors
3. ARMD studies
4. Prevention
5. Treatment options
6. Low vision care
7. Resources

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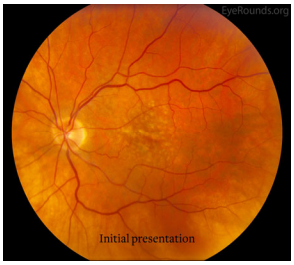
Age-related macular degeneration (ARMD)

A medical condition which may result in blurred or no vision in the center of the visual field.

1. **Dry ARMD**
2. **Intermediate ARMD**
3. **Geographic atrophy**
4. **Wet ARMD**

Dry ARMD

- Disruption of the RPE
- Drusen
- Loss of photoreceptors



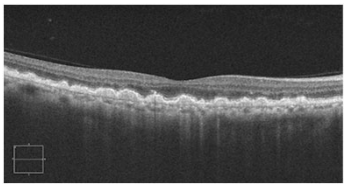


Fig. 1. Early AMD (AREDS Category 2) from: "Age-related macular degeneration", webeye.ophth.uiowa.edu/eyeforum/atlas/pages/AMD.htm. Accessed Dec 2022.

Fig. 2. Drusen appear as lumps underneath the RPE from: "How to diagnose and manage macular degeneration", Jan 2019, eyeguru.org/essentials/guide-to-amd/. Accessed Dec 2022.

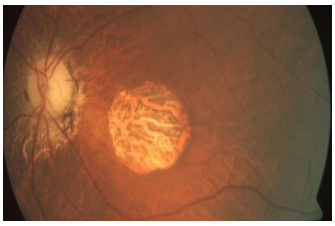
Intermediate ARMD

- Extensive drusen of small or intermediate size, or any drusen of large size (≥125 microns)
- RPE disruption
- Increased visual symptoms

Fig. 1. Dry AMD with drusen collected under the retina in the macula from: "Age related macular deneration", www.rvscny.com/patient-eduction/conditions-we-treat/age-related-macular-degeneration//. Accessed Dec 2022.

Geographic atrophy

- Loss of photoreceptors/RPE
- Variable central vision loss



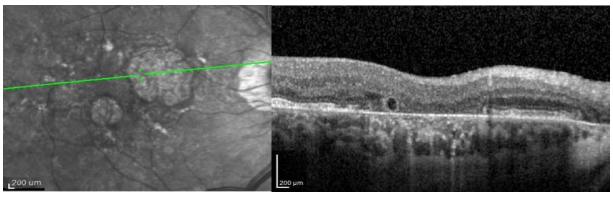
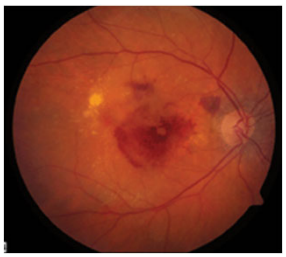


Fig. 1. Geographic atrophy treatment with APL-2 from: Webeyeclinic.com, www.webeyeclinic.com/age-related-macular-degeneration/geographic-atrophy-treatment/. Accessed Dec 2022.

Fig. 2. SD-OCT imaging of an ORT in a 76-year-old subject with nonexudative AMD., www.researchgate.net/figure/SD-OCT-imaging-of-an-ORT-in-a-76-year-old-subject-with-nonexudative-AMD-A-Infrared_fig1_311705040. Accessed Dec 2022.

Wet ARMD

- Neovascular membrane
- Leakage of blood and serum
- Affects multiple layers of sensory retina
- Progressive vision loss



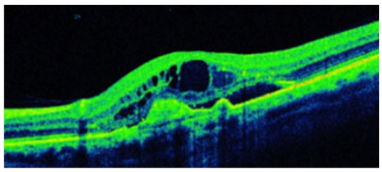


Fig. 1. Role of Advanced Retinal Imaging in Management of Neovascular AMD, macular degen from: Box Hill eye surgeons, boxhilleyesurgeons.com.au/role-advanced-retinal-imaging-management-neovascular-amd/macular_degen/. Accessed Dec 2022.

Fig. 2. Role of Advanced Retinal Imaging in Management of Neovascular AMD, from: Box Hill eye surgeons, boxhilleyesurgeons.com.au/role-advanced-retinal-imaging-management-neovascular-amd/. Accessed Dec 2022.

Risk factors

Non-modifiable

- Age
- Female
- Family history
- Light iris color
- Hyperopia
- Inflammatory markers

Modifiable

- Smoking
- Obesity
- Vascular disease
- Hypertension

ARMD studies – National Eye Institute

AREDS 1

- 4747 people aged 55-80
- 1992-1996
- Follow-up Q6m for at least 7 years
- High dose antioxidant vitamins and zinc (AREDS1 vitamins) showed a 34% reduction in vision loss in those patients at high risk

AREDS 2

- 4203 people
- 2006-2012
- Addition of lutein and zeaxanthin
- Removal of beta-carotene
- Addition of omega-3 fatty acids
- Reduction of zinc

Prevention

- **Stop smoking**
- **Improve diet**
- **Supplements**
- **Control blood pressure**
- **Physical fitness and exercise**

Treatment options for wet ARMD

Traditional

- Thermal laser
- Photo dynamic therapy

Current

- Anti-vascular endothelial growth factor (VEGF) injections
  - Bevacizumab – Avastin®
  - Ranibizumab – Lucentis®, Susvimo®/PDS
  - Aflibercept – Eylea®
- VEGF + Angiopoietin-2 inhibitor
  - Faricimab-svoa – Vabysmo®

Treatment for geographic atrophy (advanced dry ARMD)

- Multiple compliment factors that lead to vision loss
- Pegcetacoplan (investigational)
- Avacincaptad pegol – Zimura® (investigational)
- Stem cells

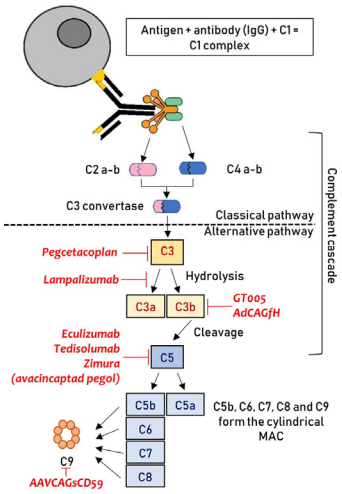


Fig. 1. Graphical representation of the complement cascade from: "Treatments for dry age-related macular degeneration: therapeutic avenues, clinical trails and future directionsbjo.bmj.com/content/106/3/297/. Accessed Dec 2022.

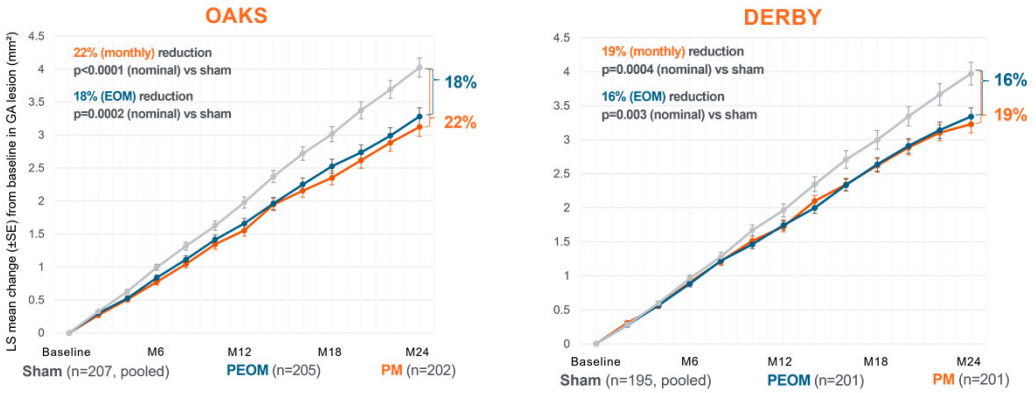
Pegcetacoplan

- Eye injections for geographic atrophy
- A C3 compliment inhibitor
- Currently FDA approved as a skin injection for paroxysmal nocturnal hemoglobinuria
- Two phase 3 trails – DERBY and OAKS show promising results

OAKS and DERBY

OAKS DERBY

Pegcetacoplan showed clinically meaningful reductions in GA lesion growth from baseline to month 24.

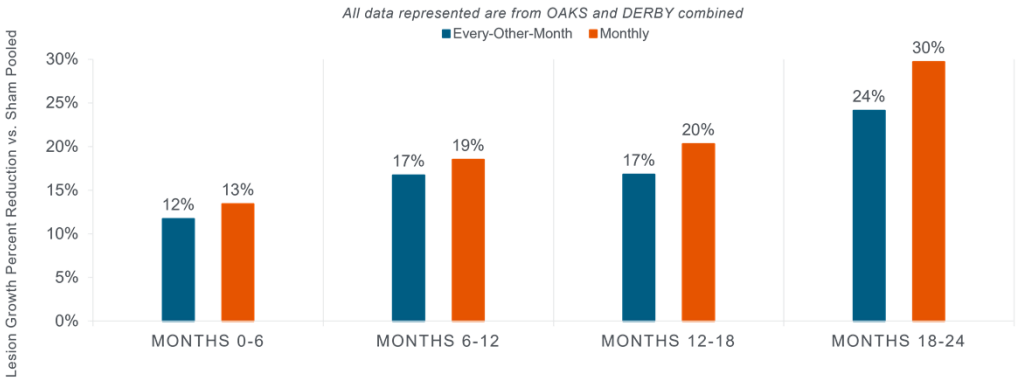


No clinically meaningful difference on key functional endpoints was observed at 24 months

SE= standard error. Least square (LS) means estimated from a mixed-effects model for repeated measures (MMRM). The mITT population was used for the analysis, defined as all randomized patients who received at least 1 injection of pegcetacoplan or sham and have baseline and at least one post-baseline value of GA lesion area in the study eye.

OAKS and DERBY

Pegcetacoplan treatment effects accelerated between months 18 and 24.



GA=geographic atrophy; Percent reduction vs. pooled sham for Month 0 to Month 24 was estimated from a piecewise linear slope model with 6-month segments using the combined patient-level data, not a simple average of results, from the two studies. All p-values are nominal. Point estimates for the Month 0 to Month 18 segments vary marginally from previously reported numbers due to the inclusion of the Month 20 to Month 24 data into the statistical model.

OAKS and DERBY conclusion

Pegcetacoplan demonstrated a favorable safety profile in OAKS and DERBY over 24 months.

Exudative AMD:
- The combined rate of new-onset eAMD at month 24 was **11.9%**, **6.7%**, and **3.1%** in the PM, PEOM, and sham groups, respectively

Infectious endophthalmitis:
- Over 24 months, the rate of infectious endophthalmitis was **0.034% per injection**
  - No cases of endophthalmitis were reported between months 18 and 24

Intraocular inflammation (IOI):
- Over 24 months, the rate of intraocular inflammation was **0.24% per injection**
  - No events of occlusive vasculitis or retinitis were observed over 24 months

- Pegcetacoplan is the first agent to show clinically meaningful reduction of GA lesion growth in two phase 3 studies
- The safety profile of pegcetacoplan is favorable
- The GALE extension study will show the long-term impact of treatment with pegcetacoplan
- FDA submission (under priority review) is ongoing, and EMA submission is planned by end of 2022

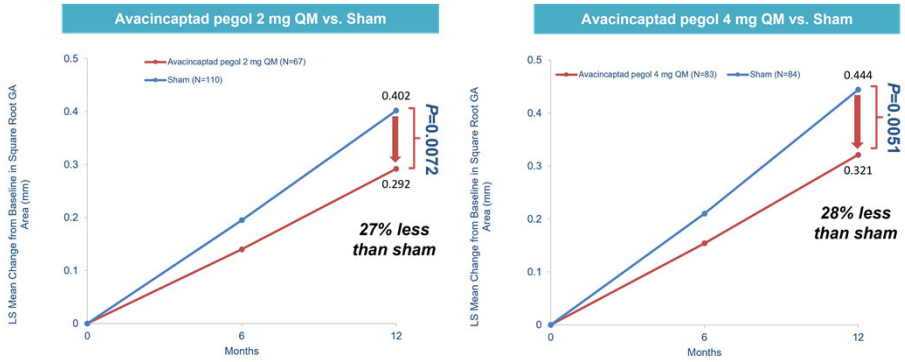
PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly.

Avacincaptad pegol

- C5 inhibitor
- Intravitreal injection
- Positive date from phase 3 gather 1 and 2 studies
  - Slows progression about 20%

GATHER1: Primary efficacy analysis

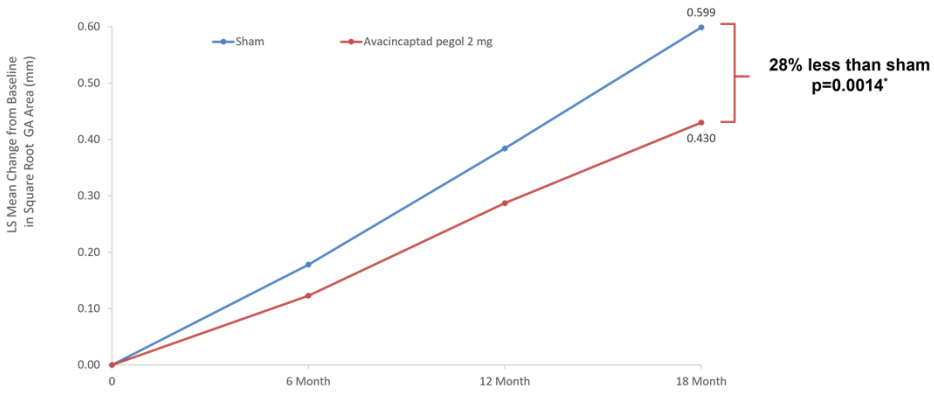
Change in square-root GA lesion area over 12 months.
Mean change from baseline in square-root GA lesion area over 12 months.



Jaffe, G., et al. (in press). C5 Inhibitor Avacincaptad Pegol for Geographic Atrophy Due to Age-Related Macular Degeneration: A Randomized Pivotal Phase 2/3 Trial. *Ophthalmology*. Retrieved from: https://www.aaojournal.org/article/S0161-6420(20)30845-9/fulltext.

GATHER1: Decrease in GA growth over 18 months

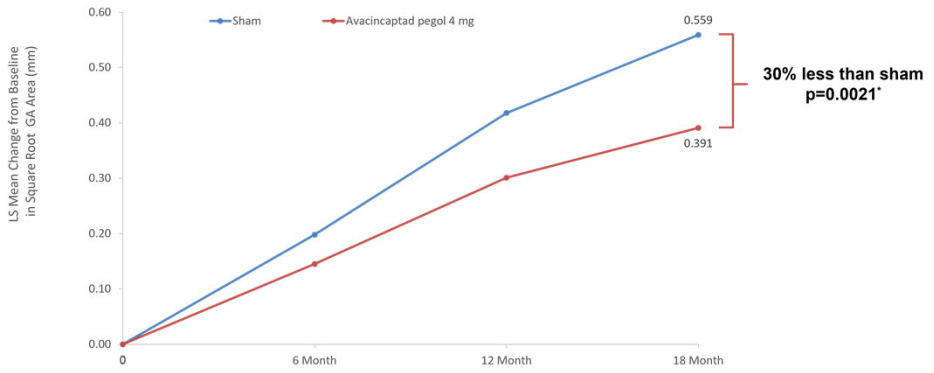
Avacincaptad pegol 2 mg vs. Sham



ITT Population; Based on LSMEANS from MRM Model, drawing on all available data, including data from groups with different randomization ratios in Part 1 and Part 2, and should not be interpreted as directly observed data; Prespecified and descriptive analysis. *18-month p values are descriptive in nature.

GATHER1: Decrease in GA growth over 18 months

Avacincaptad pegol 4 mg vs. Sham



ITT Population; Based on the least squares means from the MRM Model drawing on all available data; Prespecified and descriptive analysis. *18-month p values are descriptive in nature.

GATHER1: Secondary endpoints

Trial not designed to demonstrate differences in mean changes in BCVA or LL BCVA with statistical significance.

Mean change in best corrected visual acuity (ETDRS letters) from Baseline to Month 18

Cohort	Avacincaptad Pegol 2 mg (N=67)	Sham (N=110)	Difference
Mean Change in BCVA[a]	-12.7[b]	-15.1[b]	2.37

Cohort	Avacincaptad Pegol 4 mg (N=83)	Sham (N=84)	Difference
Mean Change in BCVA[a]	-4.27	-7.07	2.80

Mean change in low luminance best corrected visual acuity (ETDRS letters) from Baseline to Month 18

Cohort	Avacincaptad Pegol 2 mg (N=67)	Sham (N=110)	Difference
Mean Change in LL BCVA[a]	-2.72[b]	-3.10[b]	0.37

Cohort	Avacincaptad Pegol 4 mg (N=83)	Sham (N=84)	Difference
Mean Change in LL BCVA[a]	2.85	1.68	1.17

a. Based on the least square means from the MRM model; ITT population.

b. These least square means are estimates of the MRM model, drawing on all available data, including data from groups with different randomization ratios in Part 1 and Part 2, and should not be interpreted as directly observed data.

GATHER1: 18-month safety analysis

- Avacincaptad pegol was generally well tolerated after 18 months of continuous administration
- No reported avacincaptad pegol-related adverse events or inflammation
- No reported avacincaptad pegol-related serious ocular adverse events or endophthalmitis in the study eye
- The most frequently reported ocular adverse events were related to the injection procedure

Incidence of study eye CNV

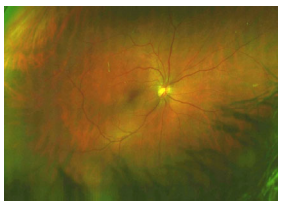
- 3 patients (2.7%) in the sham group
- 2 patients (7.7%) in the avacincaptad pegol 1 mg group
- 8 patients (11.9%) in the avacincaptad pegol 2 mg group
- 13 patients (15.7%) in the avacincaptad pegol 4 mg group

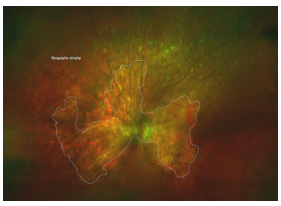
Low vision care

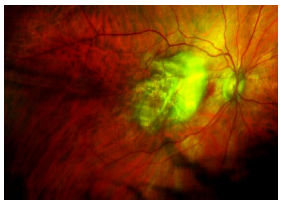
- Central blind spot
- Magnification
- Rehabilitation

Macular degeneration

A break down of one of more elements of the central retina leading to loss of central visual function.



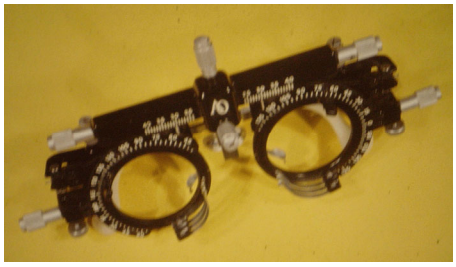




SA Edmonds. Photos from clinical collection.

Trial frame

- Allows head movements
- Maximizes eccentric viewing
- Variable difference between lens choices "one and two"



SA Edmonds. Photo from clinical collection.

Hand-held lens testing

Spheres

-0.50 vs +0.50

-1.00 vs +1.00

-2.00 vs +2.00

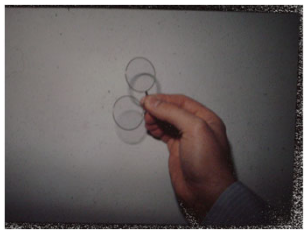
-5.00 vs +5.00

-10.00 vs +10.00

Cylinder

+/- 0.50

+/- 1.00



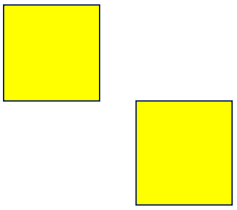
SA Edmonds. Photos from clinical collection.

Principle of just-noticeable difference (JND)

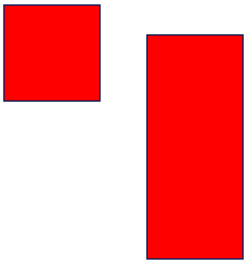
In the branch of experimental psychology focused on sense, sensation, and perception, which is called psychophysics, a just-noticeable difference (JND) is the amount something must be changed in order for a difference to be noticeable, detectable at least half the time (absolute threshold).

Which image is square?

One or two



One or two



Magnification

- Testing with magnification will determine the direction of the management plan
- Positive response indicates discrete central loss
  - Will be best managed with magnification aid and eccentric viewing rehabilitation
- Negative response indicates a diffuse loss of vision and magnifiers are contraindicated
  - Must use aids for precise light and contrast enhancement

Magnification applications

- Once the correct magnification is calculated, function testing is used to verify and fine tune the best magnification
- Magnification can then be applied with a host of options
  - Microscope
  - Telescope
  - Optical devices
    - Hand-held
    - Stand
    - Lighted
    - Electronic

Other rehabilitation programs

Field loss (glaucoma, stroke, brain injury)
- Yoked prism
- Peli prism
- Eye movement therapy

Eye movement disorders (concussion, brain injury, glaucoma)
- Orthoptics
- Saccade therapy
- Smooth pursuit therapy

External resources

- Orientation and mobility training
  - Cane travel
  - Guide dog program (TAZ)
- Braille and auditory education
- Occupational therapy
  - Independent living skills
- Vision aware program
  - Adjustment to vision loss
  - Adaptive home
  - Daily living skills
  - Guides for family and friends