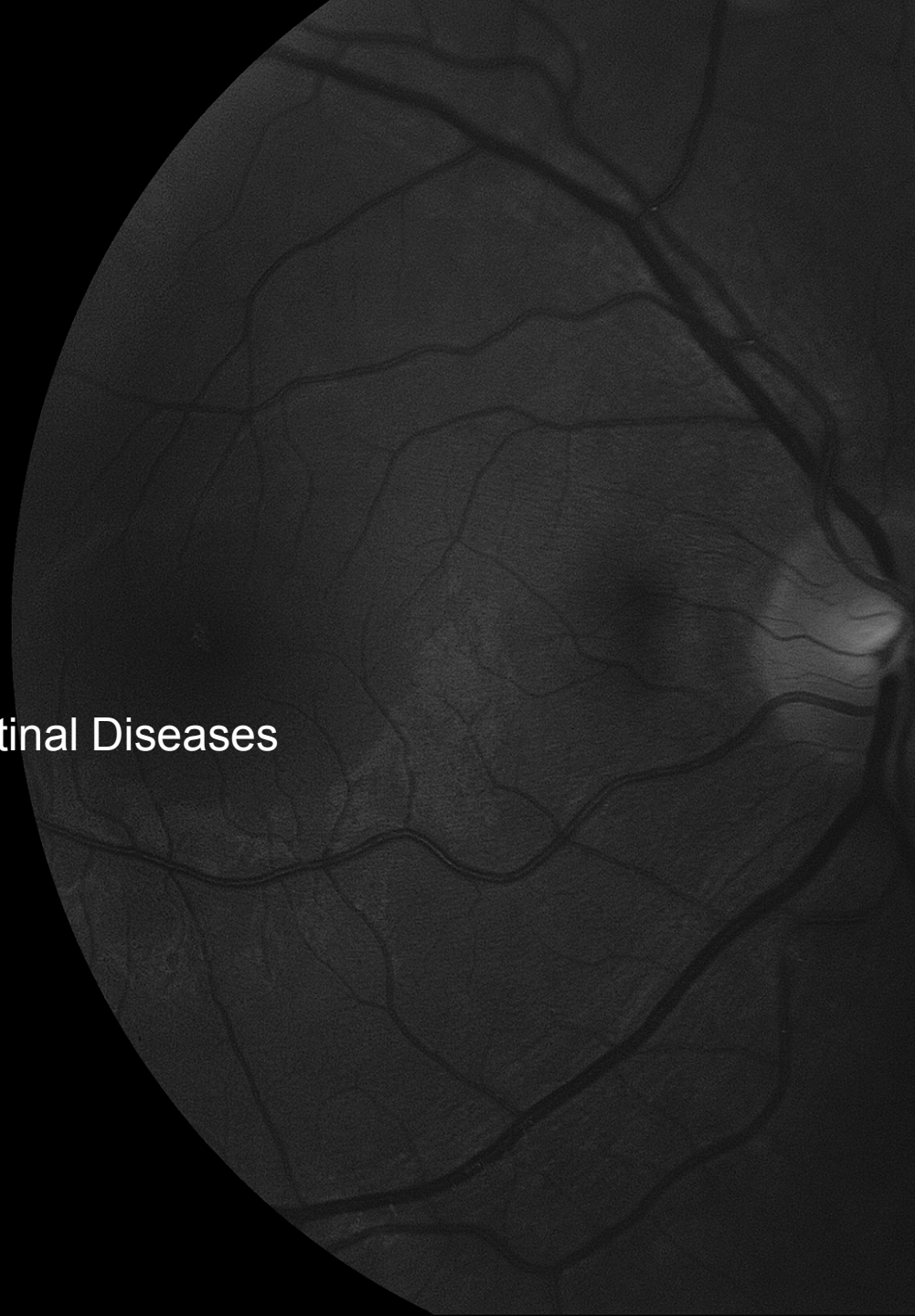
IVERIC bio

Developing Transformative Therapies for Retinal Diseases

Glenn P. Sblendorio
Chief Executive Officer and President



November 2019
NASDAQ: ISEE

Forward-looking Statements

Any statements in this presentation about the Company's future expectations, plans and prospects constitute forward-looking statements for purposes of the safe harbor provisions under the Private Securities Litigation Reform Act of 1995. Forward-looking statements include any statements about the Company's strategy, future operations and future expectations and plans and prospects for the Company, and any other statements containing the words "anticipate," "believe," "estimate," "expect," "intend", "goal," "may", "might," "plan," "predict," "project," "seek," "target," "potential," "will," "would," "could," "should," "continue," and similar expressions. In this presentation, the Company's forward looking statements include statements about its expectations to use its previously announced clinical trial of Zimura for the treatment of geographic atrophy as a pivotal trial, its development strategy for Zimura, the Company's hypotheses regarding complement inhibition as a mechanism of action for the treatment of geographic atrophy, the projected use of cash and cash balances, the timing, progress and results of clinical trials and other research and development activities, the potential utility of its product candidates, estimates regarding the number of patients affected by the diseases and indications the Company's product candidates are intended to treat, and statements regarding the potential for the Company's business development strategy. Such forward-looking statements involve substantial risks and uncertainties that could cause the Company's development programs, future results, performance or achievements to differ significantly from those expressed or implied by the forward-looking statements. Such risks and uncertainties include, among others, those related to the initiation and the progress of research and development programs and clinical trials, availability of data from these programs, reliance on university collaborators and other third parties, establishment of manufacturing capabilities, expectations for regulatory matters, need for additional financing and negotiation and consummation of business development transactions and other factors discussed in the "Risk Factors" section contained in the quarterly and annual reports that the Company files with the Securities and Exchange Commission. Any forward-looking statements represent the Company's views only as of the date of this presentation. The Company anticipates that subsequent events and developments will cause its views to change. While the Company may elect to update these forward-looking statements at some point in the future, the Company specifically disclaims any obligation to do so except as required by law.

IVERIC bio Pipeline

Therapeutics

Indication	Research	Pre-clin.	Phase 1	Phase 2	Pivotal	Milestones
GA secondary to Dry AMD Zimura * Option to in-license resulting IP						• Positive topline data reported for first of two pivotal trials • Initiating second pivotal trial and plan to begin enrolling **1Q 2020**
Stargardt Disease (STGD1) Zimura						• Top-line data expected in **2H 2020**
GA secondary to Dry AMD HtrA1 Inhibitor						• Plan to file IND in **2021**

Gene Therapy

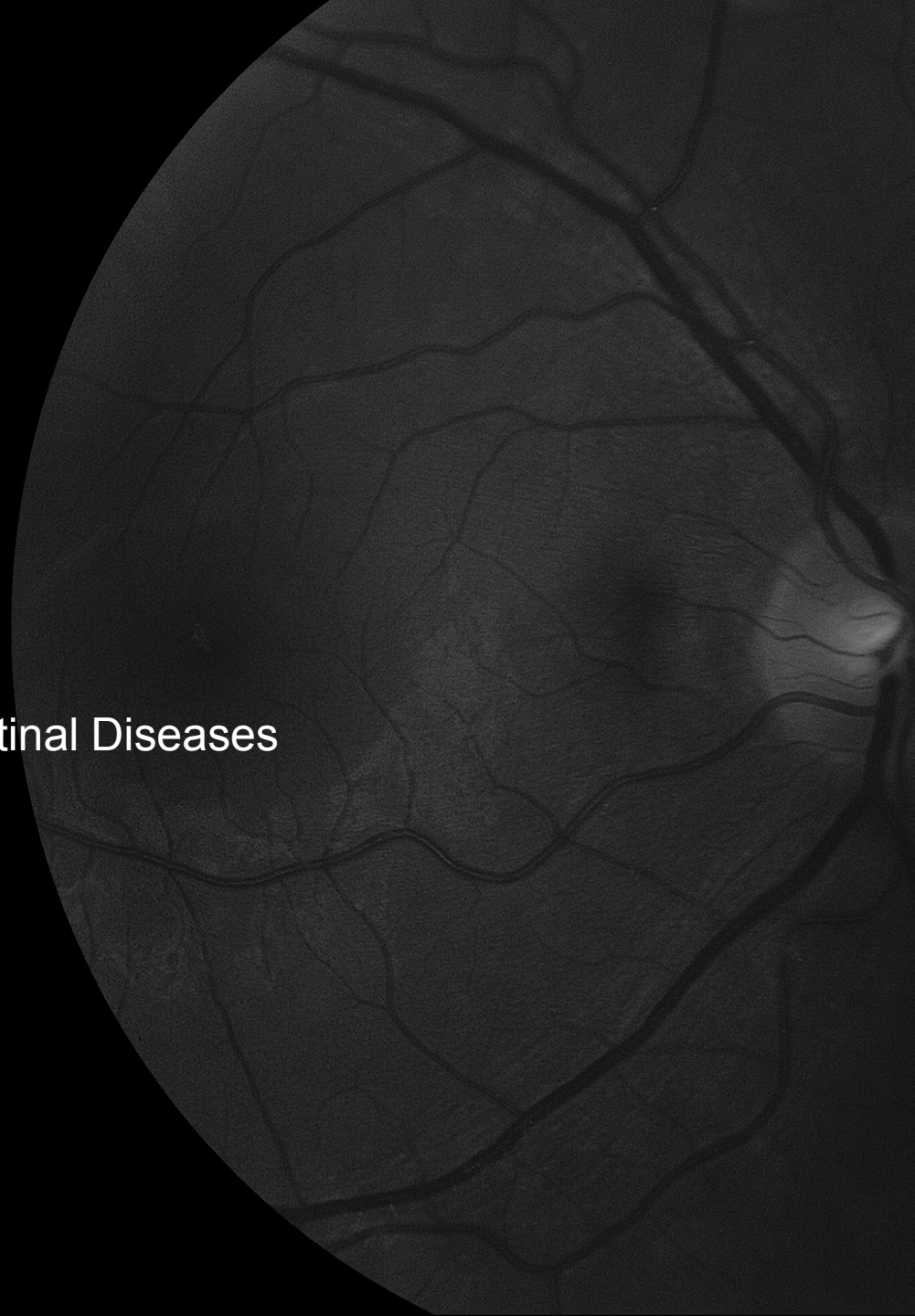
Indication	Research	Pre-clin.	Phase 1	Phase 2	Pivotal	Milestones
IC-100: RHO-adRP AAV vector						• Plan to initiate Phase 1/2 in **2H 2020**
IC-200: *Best1* Related Retinal Diseases AAV vector						• Plan to initiate Phase 1/2 in **1H 2021**
LCA10 miniCEP290 AAV "minigene" vector						• Update on lead construct early **2020**
STGD1 miniABCA4 AAV "minigene" vector						• Research results expected in early **2020***
Usher 2a miniUSH2A AAV "minigene" vector						• Recently commenced*

*We have an option to exclusively in-license intellectual property resulting from ongoing sponsored research.

IVERIC bio

Developing Transformative Therapies for Retinal Diseases

Kourous A. Rezaei, MD
Chief Medical Officer



November 2019
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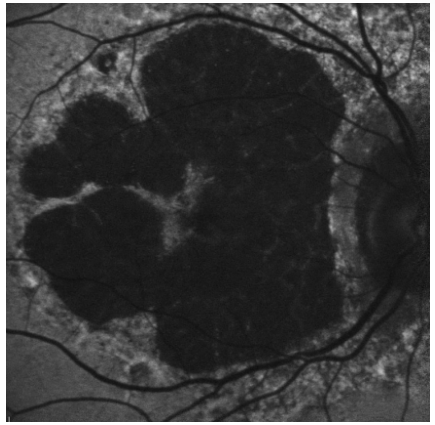
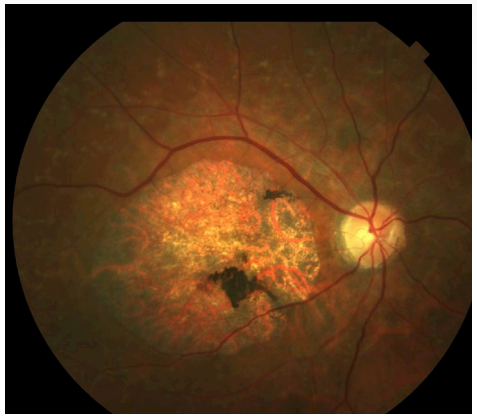
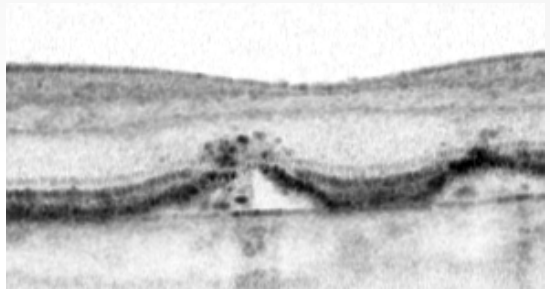
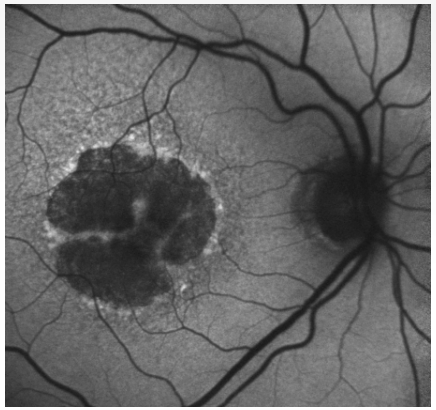
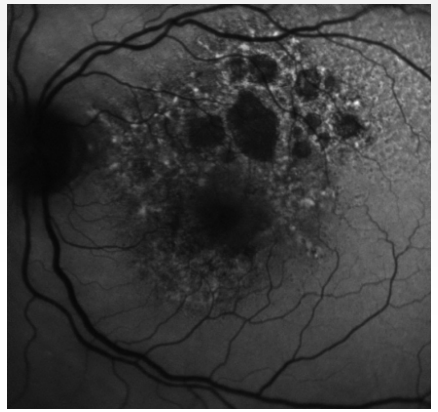
New York , Nov 20 2019

Geographic Atrophy Secondary to Dry AMD: A True Epidemic

Jordi Monés MD, PhD

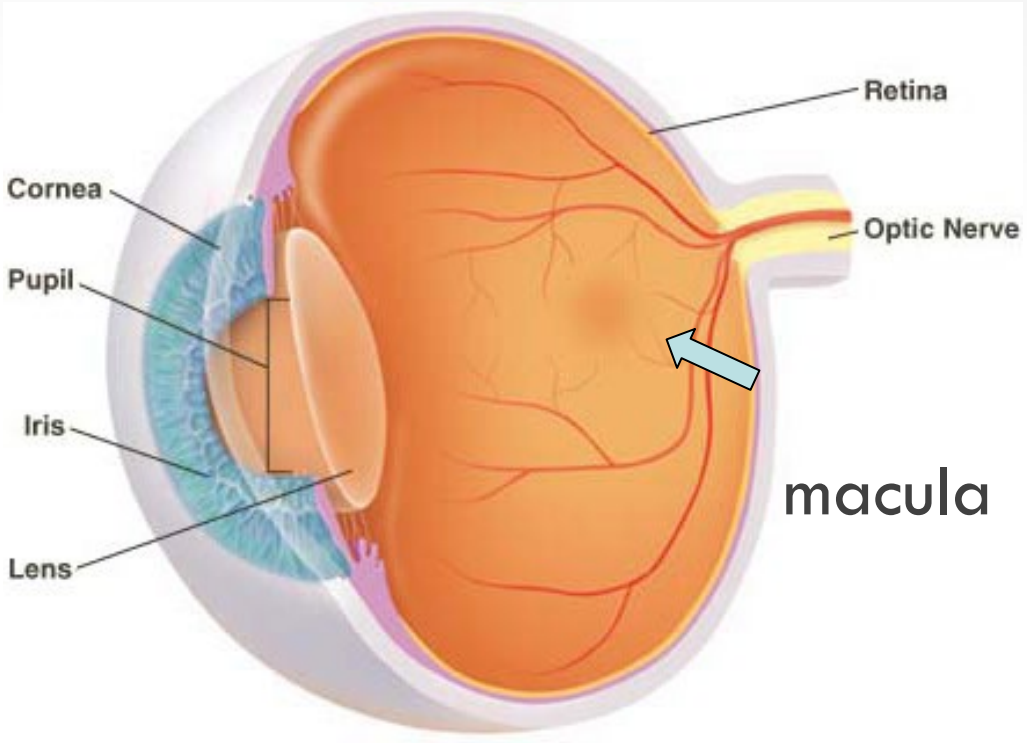
Institut de la Macula I de la Retina

Barcelona Macula Foundation

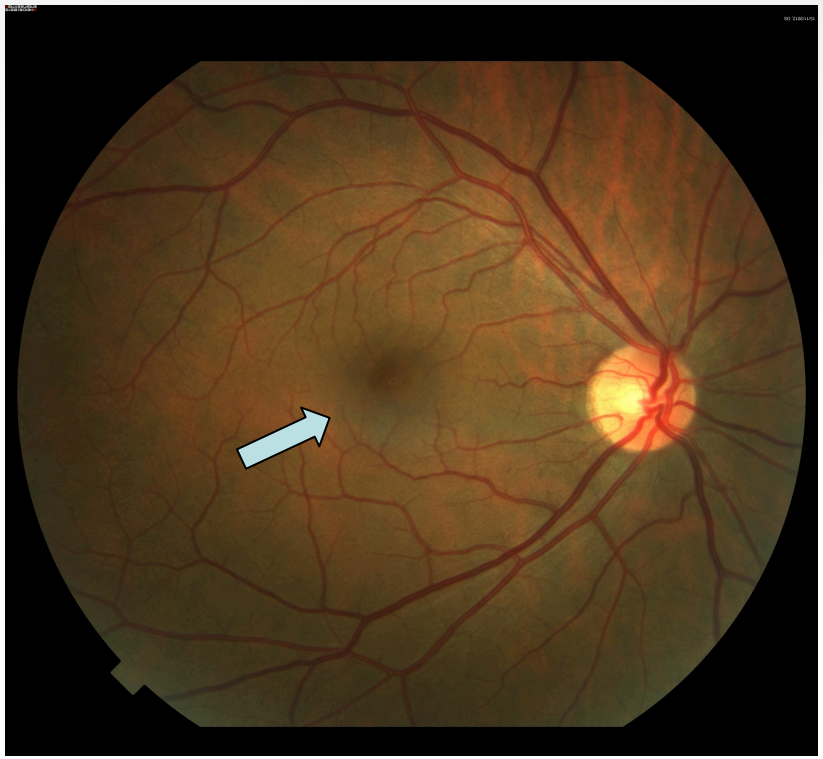
INSTITUT DE LA MÀCULA
Innovating Eye Care

BMF Barcelona Macula Foundation
Research for Vision

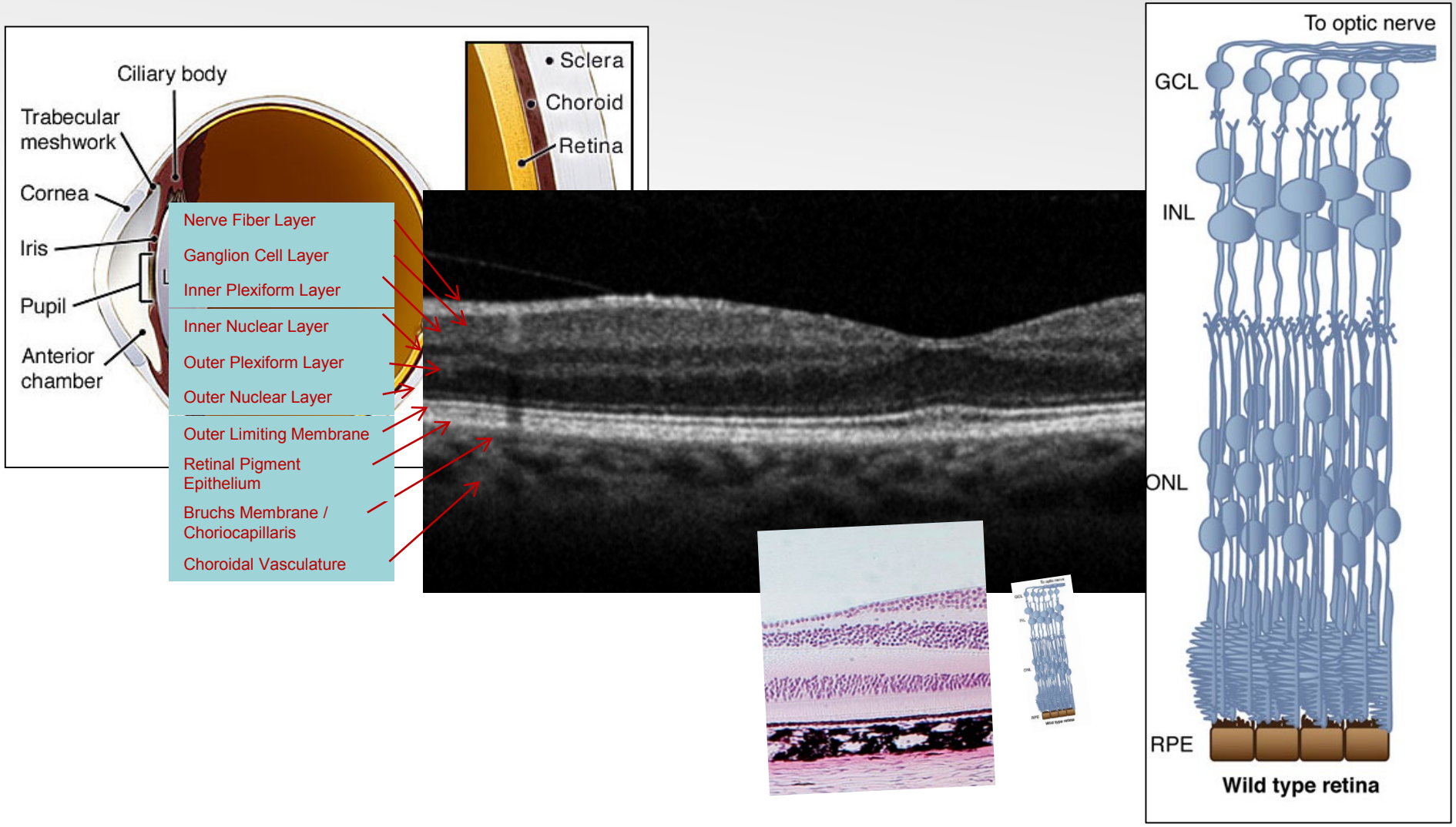
Retinal anatomy



macula

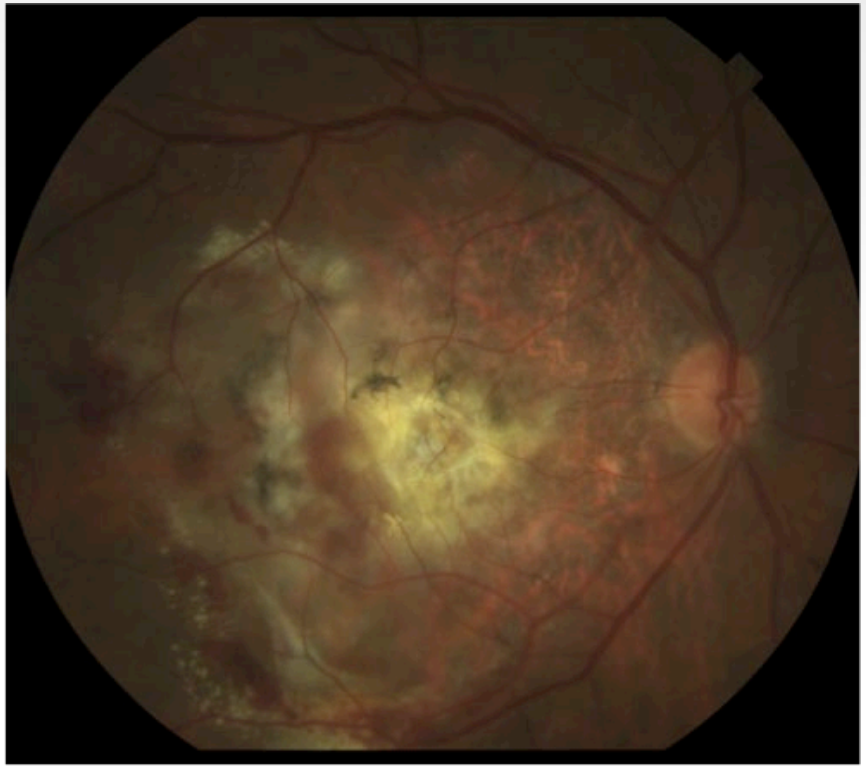


Retinal anatomy



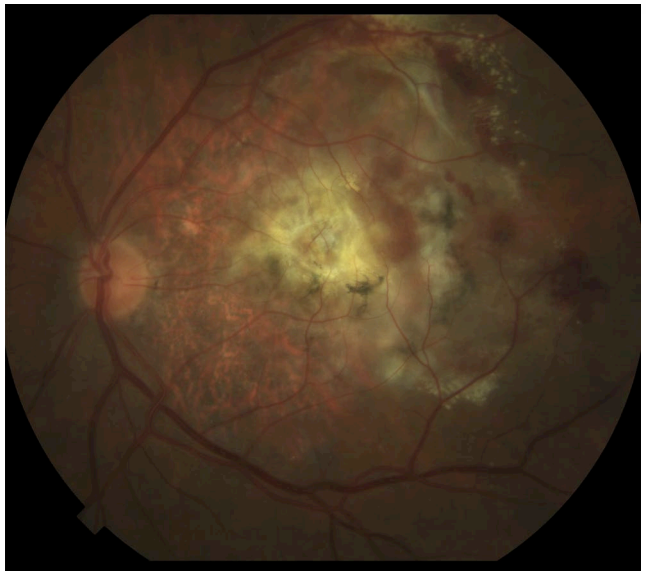
Normal fundus

Age-related macular degeneration



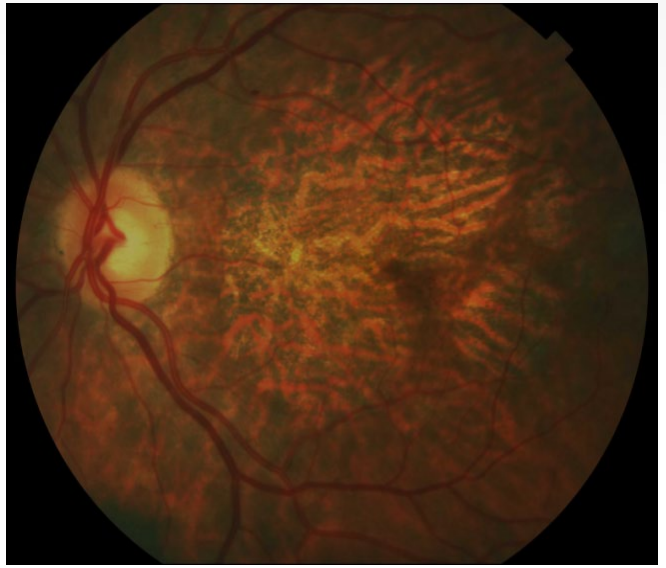
Age-related macular degeneration (AMD)

Classically advanced AMD is classified into two general subgroups: the non-neovascular (atrophic or dry) type and the neovascular (exudative or wet).



Exudative or wet

Normal



Atrophic or dry

BECKMAN CLASSIFICATION AMD

Table 2. Proposed AMD Clinical Classification

Classification of AMD	Definition (lesions assessed within 2 disc diameters of fovea in either eye)
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Late AMD	Neovascular AMD and/or Any geographic atrophy

AMD = age-related macular degeneration.
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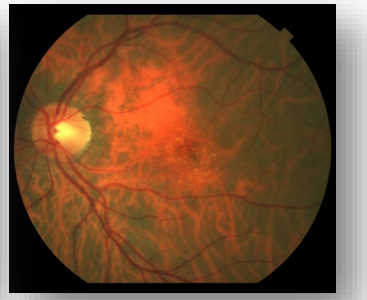
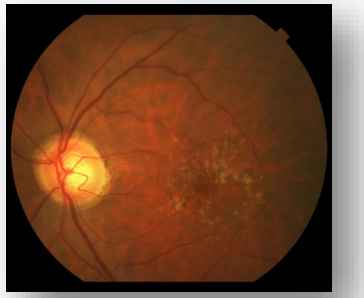
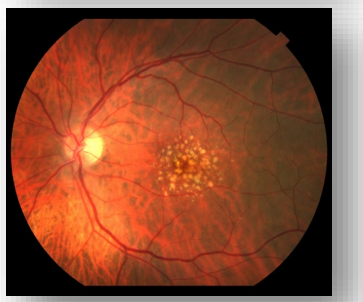
AGING CHANGES

EARLY AMD

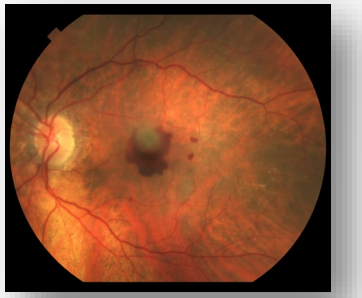


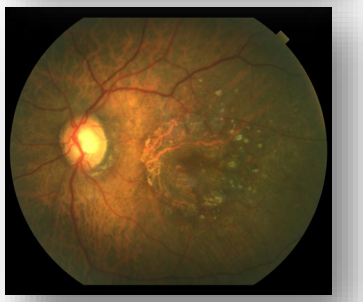
INTERMEDIATE AMD





LATE AMD





Atrophic AMD

…geographic atrophy progresses with a mean of 1.5 to 2.8 mm^2/year…

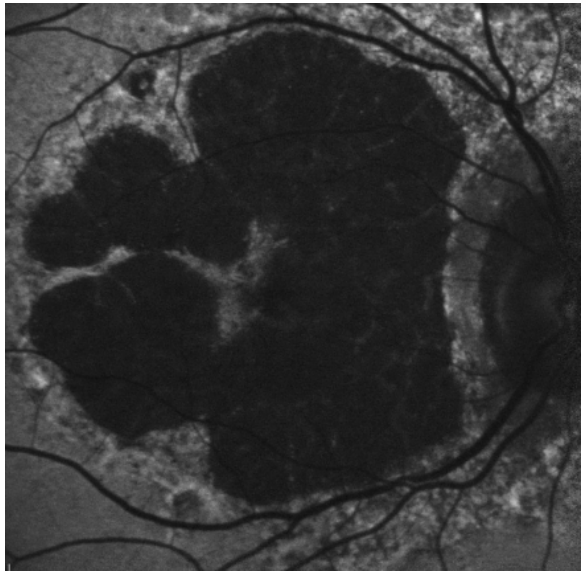
Atrophic AMD

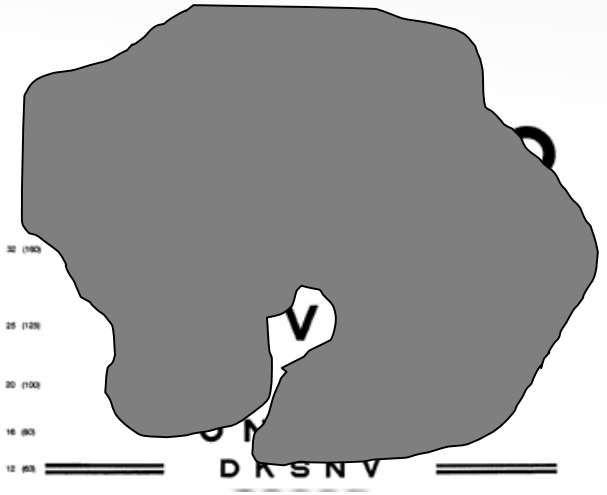
…and there is NO treatment available…

Visual function in atrophic AMD

Visual function disability underestimated…

…visual acuity a poor endpoint…





Visual function in atrophic AMD

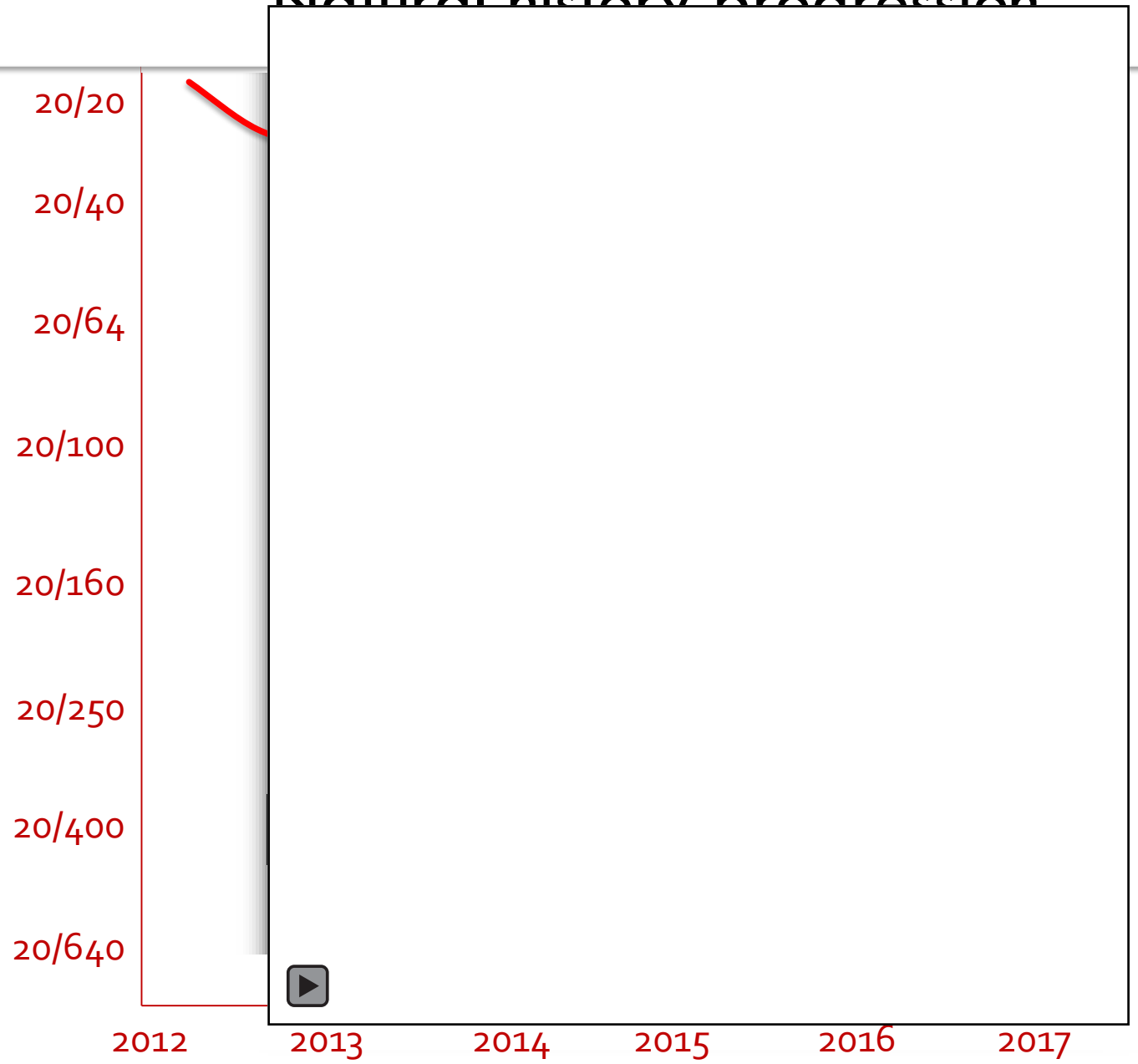
Although VA under estimated short-term decline in visual function:

- **30% 3 lines VA loss by 2 years**
- **55% 3 lines VA loss by 4 years**

- **25% of eyes with 20/50 or better decline to 20/200 or worse by 4 years**

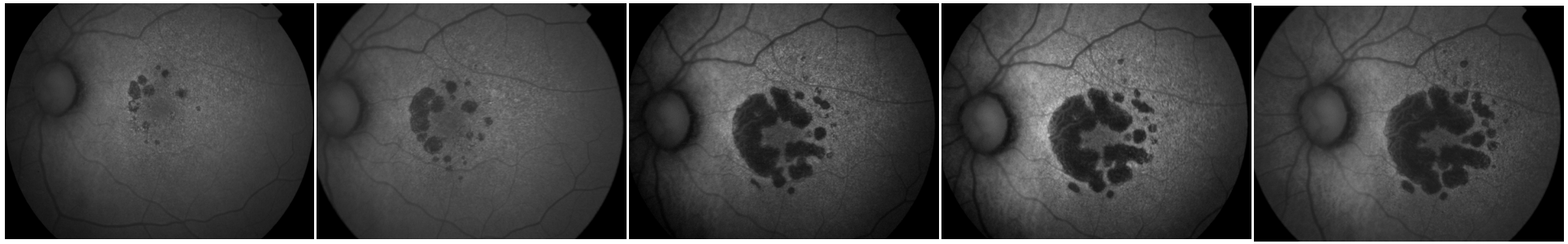
Enlargement of atrophy and visual acuity loss in the geographic atrophy form of age-related macular degeneration Sunness, Janet S. et al. Ophthalmology, Volume 106, Issue 9, 1768 - 1779

Natural history progression



Impact in quality of life

Patients with 20/200 or worse vision in one eye would trade 1 of 3 remaining years to avoid the same scenario in the fellow eye

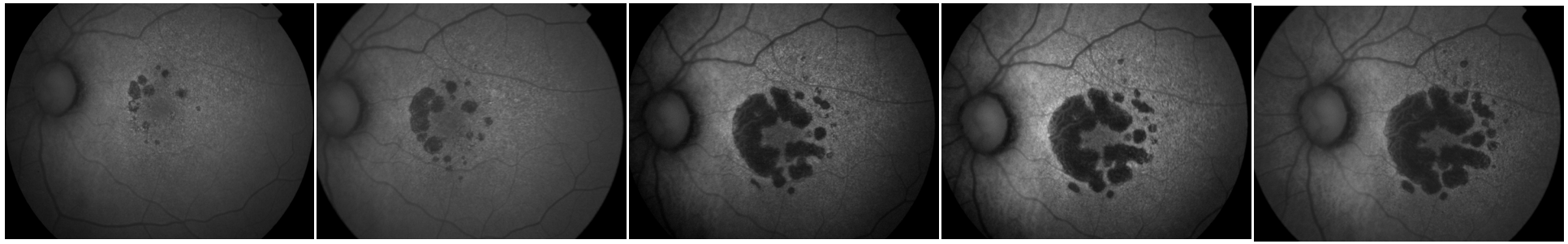


Brown MM, Brown GC, Sharma S, Kistler J, Brown H. Utility values associated with blindness in an adult population. *Br J Ophthalmol*. 2001;85(3):327–331. doi:10.1136/bjo.85.3.327

A true epidemic

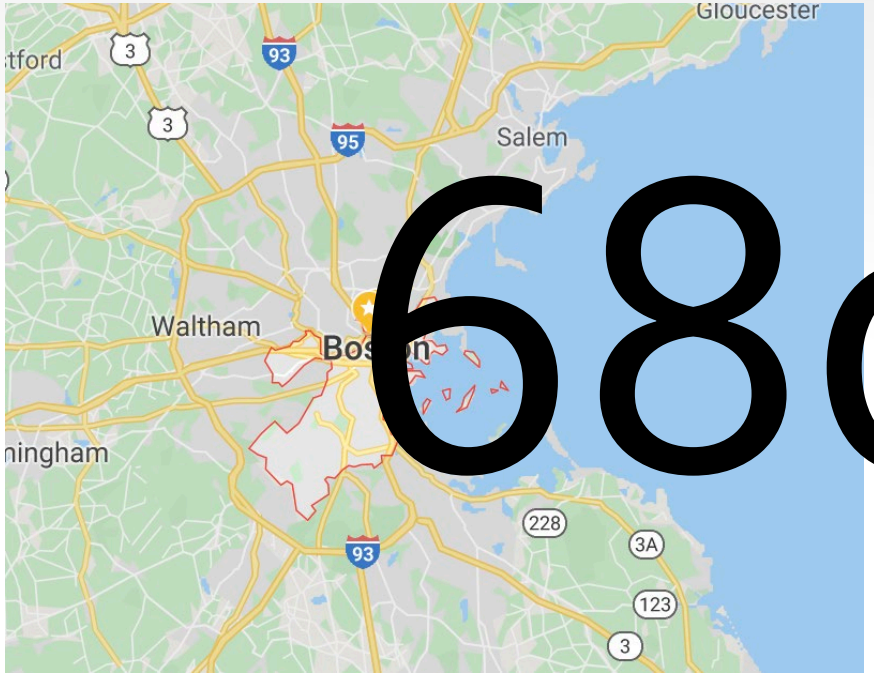
…Patients are diagnosed earlier and are living longer:

representing a true epidemic…



A true epidemic

City of Boston



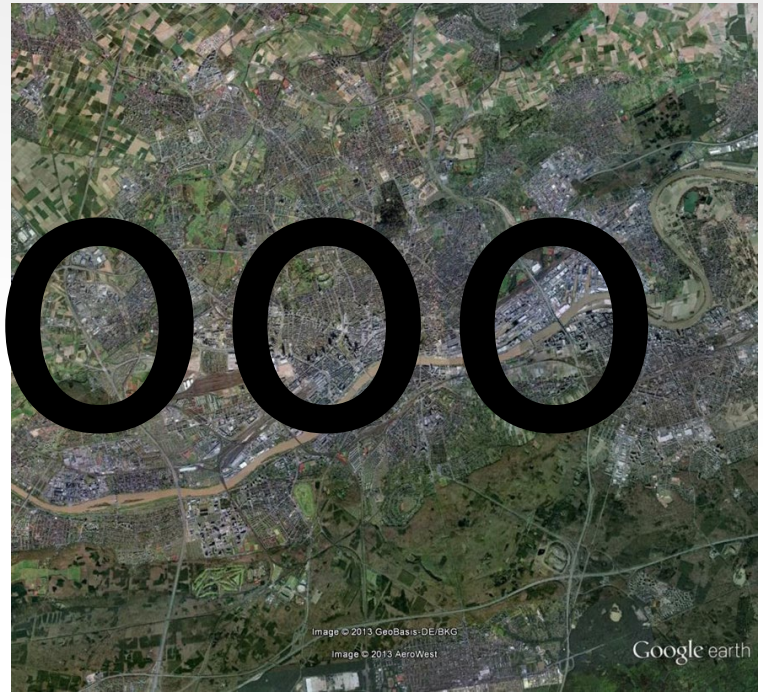
680.000

…current incidence in USA 300.000 new cases per year, half of the population of Boston

A true epidemic

City of Frankfurt, Germany

700.000



…or the annual incidence of any LATE AMD in Europe in 2050, today

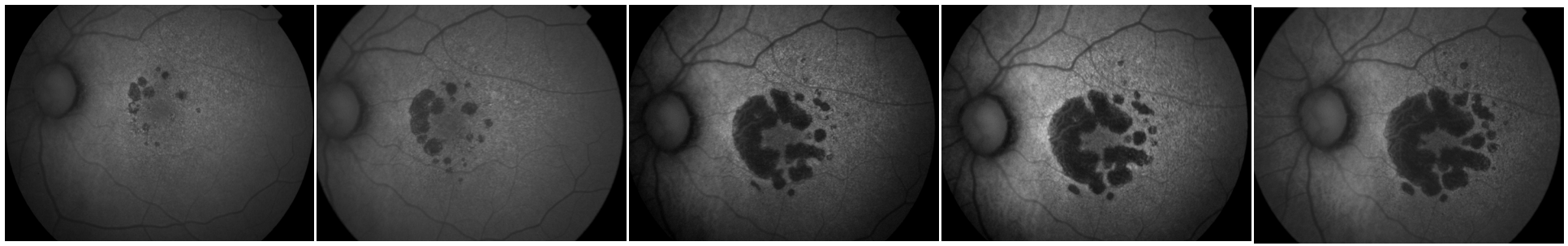
400.000

Atrophic AMD

Prevalence estimates of any AMD

2015: up to 67 million Europe / 196 million world

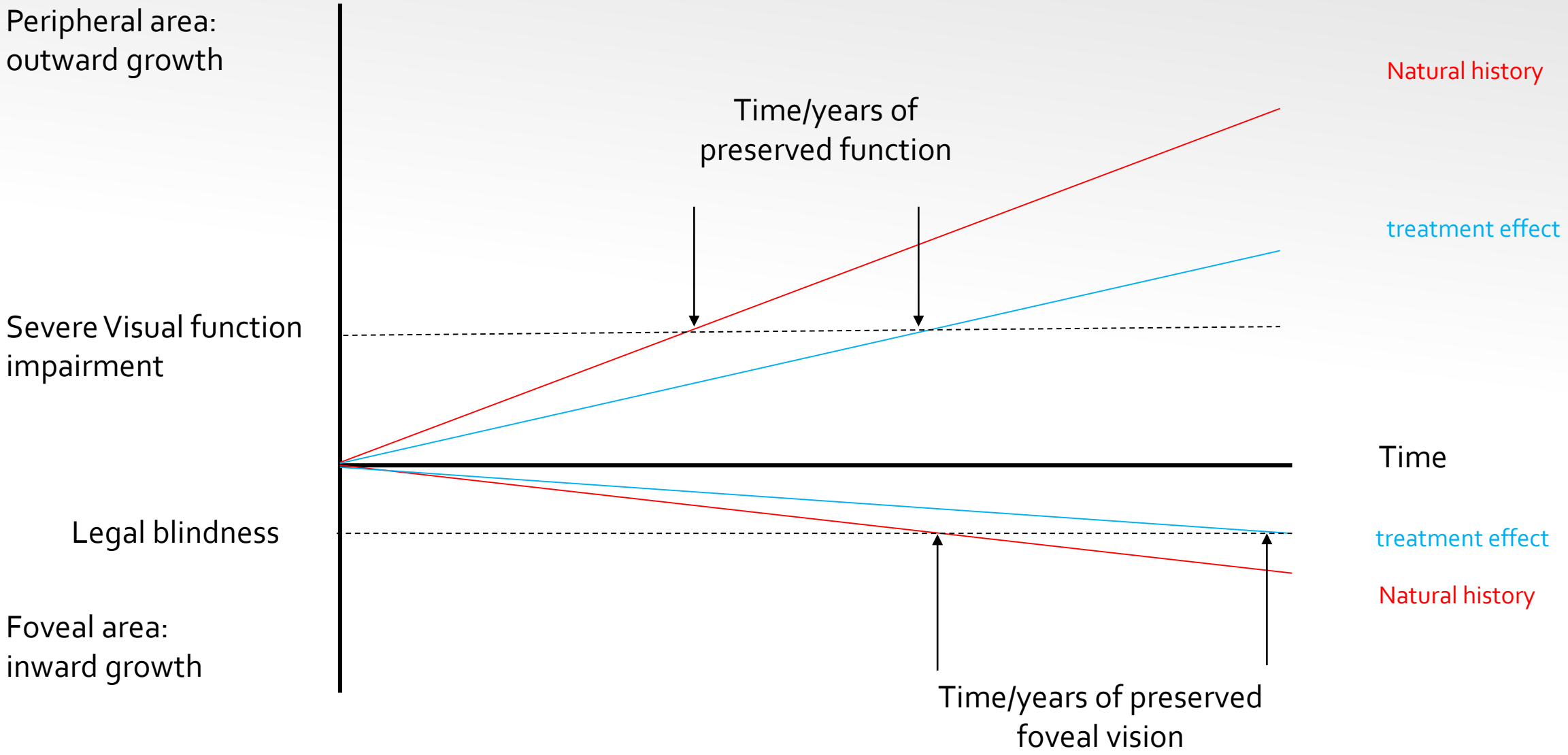
2050: up to 77 million Europe / 288 million world



Li JQ, Welchowski T, Schmid M, et al Prevalence and incidence of age-related macular degeneration in Europe: a systematic review and meta-analysis. British Journal of Ophthalmology Published Online First: 11 November 2019. doi: 10.1136/bjophthalmol-2019-314422

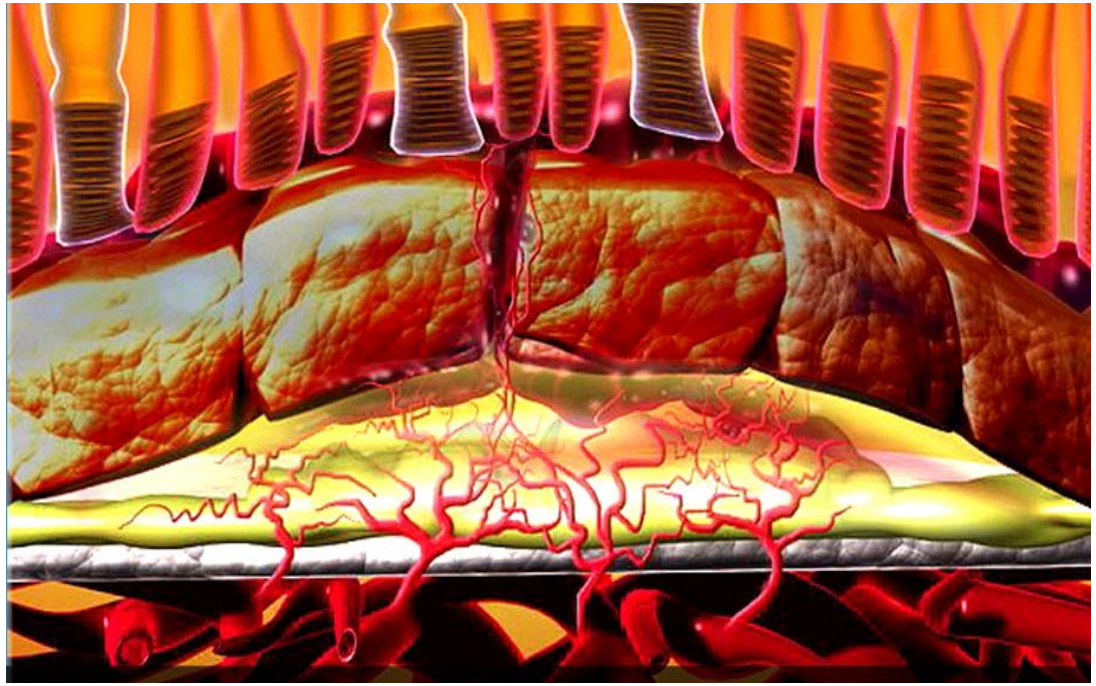
Wong, W.L., et al., Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. Lancet Glob Health, 2014. 2(2): p. e106-16.

Reduction of progression: years/vision saving



Exudative or wet AMD

Hallmark of wet AMD are new vessels that “invade” the outer retina as a reparative response, as an attempt to generate a second choriocapillaris, although ineffective and detrimental



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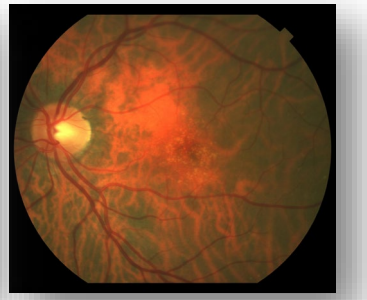

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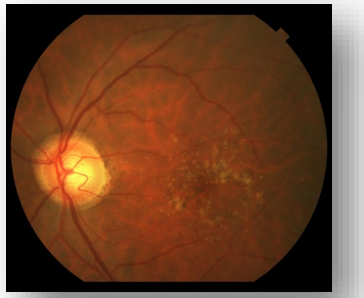
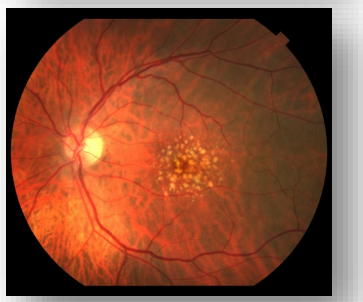
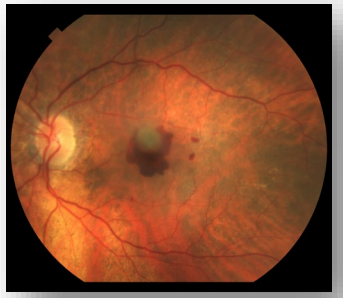
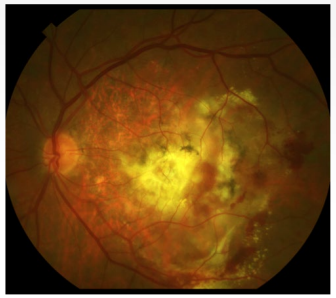
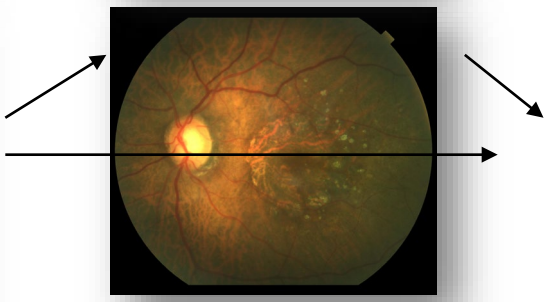




LATE AMD







Thank You!

Zimura Pivotal Trial: Design and Outcome

Kourous A. Rezaei, MD
Chief Medical Officer

November 2019
NASDAQ: ISEE

Pivotal Trial Highlights

Zimura Pivotal Trial in geographic Atrophy Secondary to AMD

- Both Zimura 2mg and 4mg were well tolerated over 12 months
- Primary efficacy endpoint was achieved for both Zimura 2mg and Zimura 4mg dose, leading to a ~27% reduction in GA growth over 12 months
- The overall data suggested a dose response relationship
- Initiating the second pivotal clinical trial with the goal of enrolling the first patient in the first quarter of 2020

Zimura Pivotal Clinical Trial for GA Secondary to Dry AMD

A Randomized, Double-Masked, Sham Controlled Trial to Assess the Safety and Efficacy of Intravitreous Administration of Zimura (Complement C5 Inhibitor) in Subjects with Geographic Atrophy Secondary to Dry Age-Related Macular Degeneration (AMD)

Screening Clinical Trial Design

- If the estimated effect size indicates low levels of benefit: would not move forward with a subsequent trial
- If the estimated effect size is moderate, but clinically relevant: move forward with subsequent Phase 3 clinical trials
- If the estimated effect size is more efficacious than the sham control with the strength of evidence meeting the level of statistical significance, as was the case in the Zimura trial for both the 2 mg and 4 mg dose groups, then the trial could potentially serve as a registration trial and only one more pivotal trial would be required for regulatory approval

Source: Fleming & Richrdson, J Infections Diseases. 2004;190:666-74.

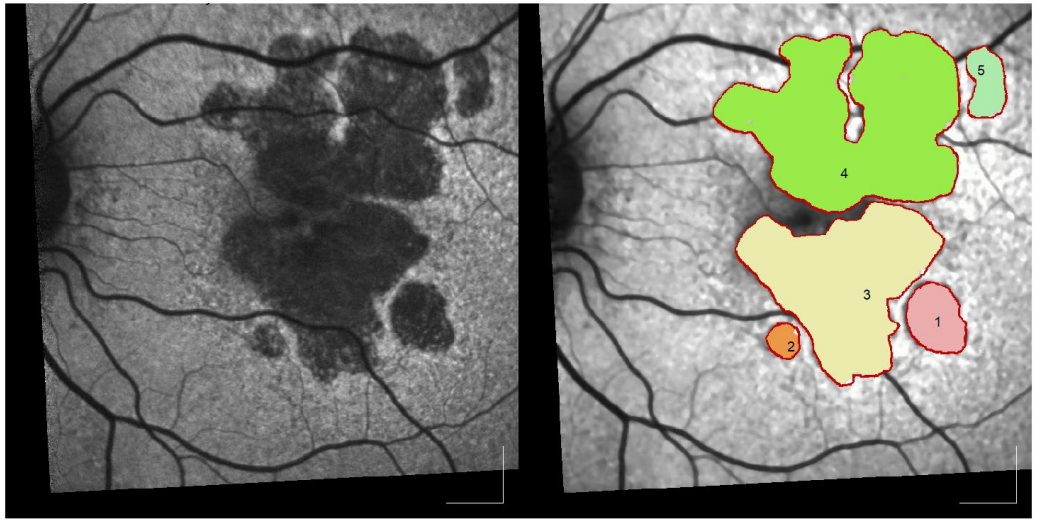
Zimura in GA Secondary to Dry AMD Pivotal Clinical Trial

- Randomized, double masked, sham controlled clinical trial
- Cohorts included in the pre-specified statistical analysis of the primary endpoint at Month 12*:
  - Zimura 4 mg dose
  - Zimura 2 mg dose
  - Sham
- 286 subjects were enrolled for monthly treatment with Zimura or Sham for 18 months
  - ~75% of the patients were enrolled in the US

*Descriptive analysis was performed for the Zimura 1mg cohort

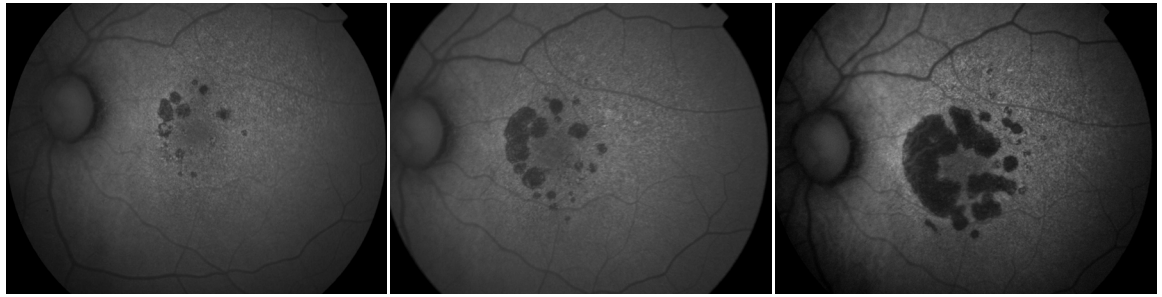
Primary Efficacy Endpoint

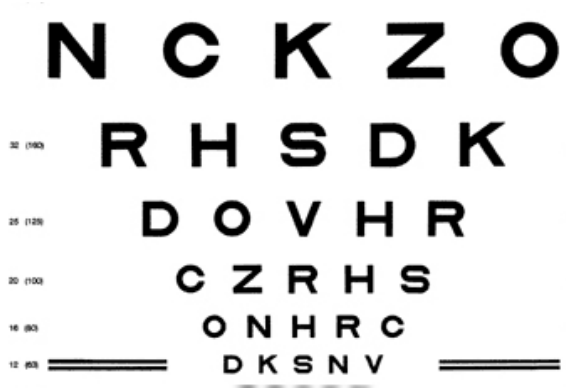
Mean rate of change in GA over 12 months measured by fundus autofluorescence (FAF) at three time points: Baseline, Month 6, and Month 12 (square root transformation of GA lesion)



Primary Efficacy Endpoint

- GA: Visual function can be a poor indicator of functional vision
- Patients' visual disabilities are usually underestimated





Courtesy: Jordi Mones, MD

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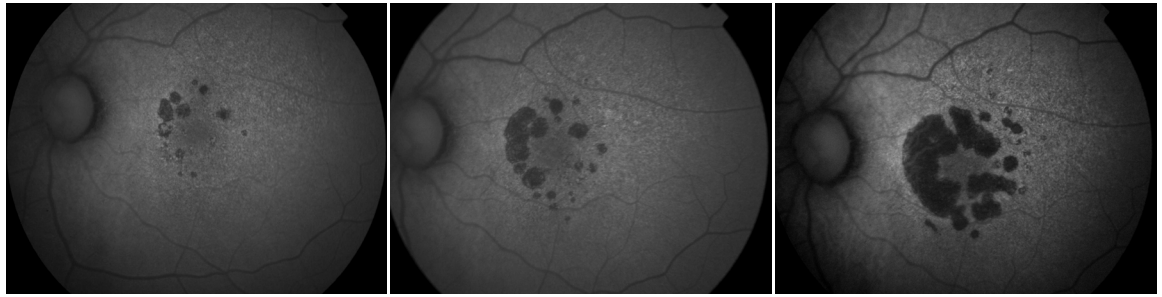
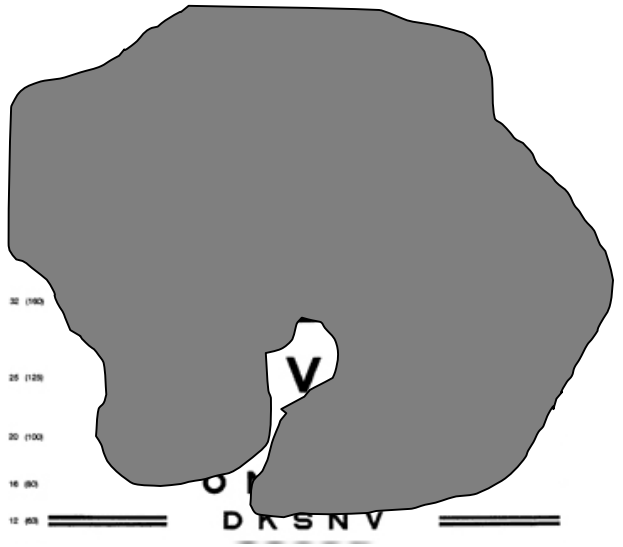
- Patients' visual disabilities are usually underestimated





Courtesy: Jordi Mones, MD

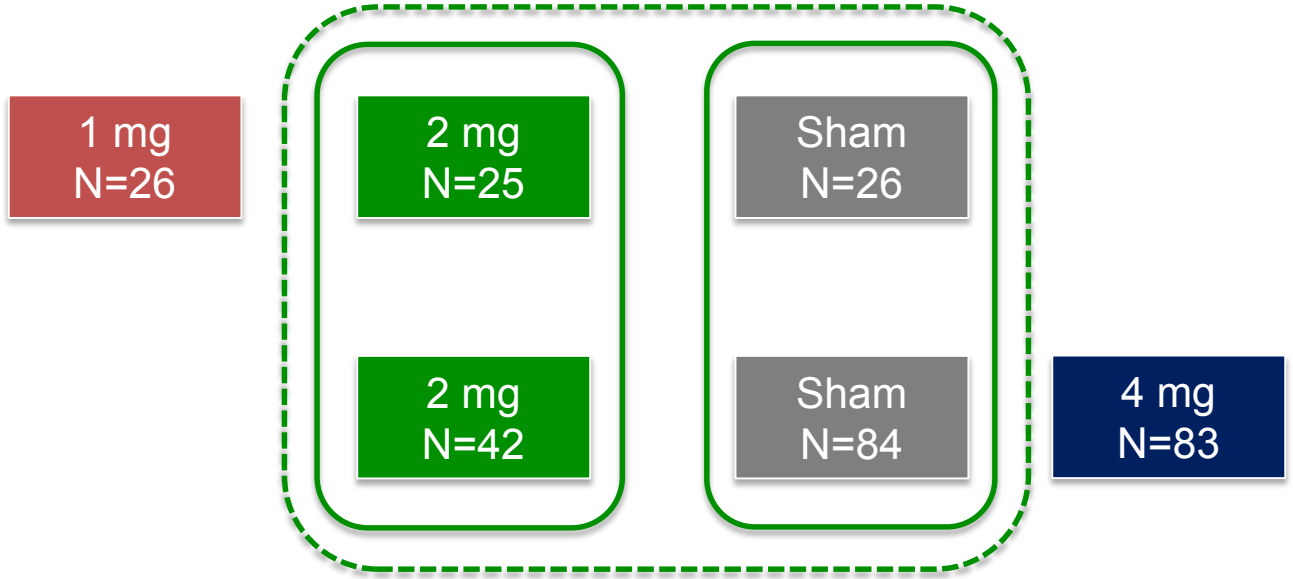
Duke Reading Center: Imaging Analysis Overview

- Completely masked assessment
- Each visit was evaluated independently
- Two experienced primary readers analyze the GA lesion size on FAF with RegionFinder
- > 10% discrepancy will be arbitrated by Reading Center Director: Glenn Jaffe, MD
- Supportive modalities: OCT and NIR imaging

Source: Duke Reading Center

Zimura in GA Secondary to Dry AMD Clinical Trial

Randomization

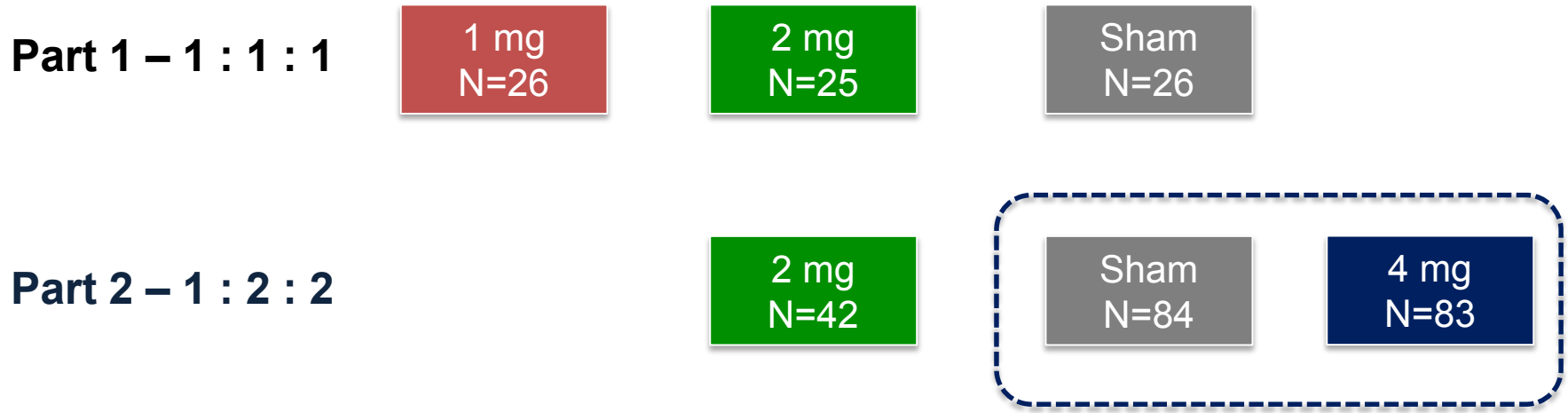


Efficacy Evaluation

- Zimura 2 mg vs. Sham: subjects randomized from Part 1 were combined with the subjects randomized to Part 2, where the analysis included a regression factor by part.

Zimura in GA Secondary to Dry AMD Clinical Trial

Randomization

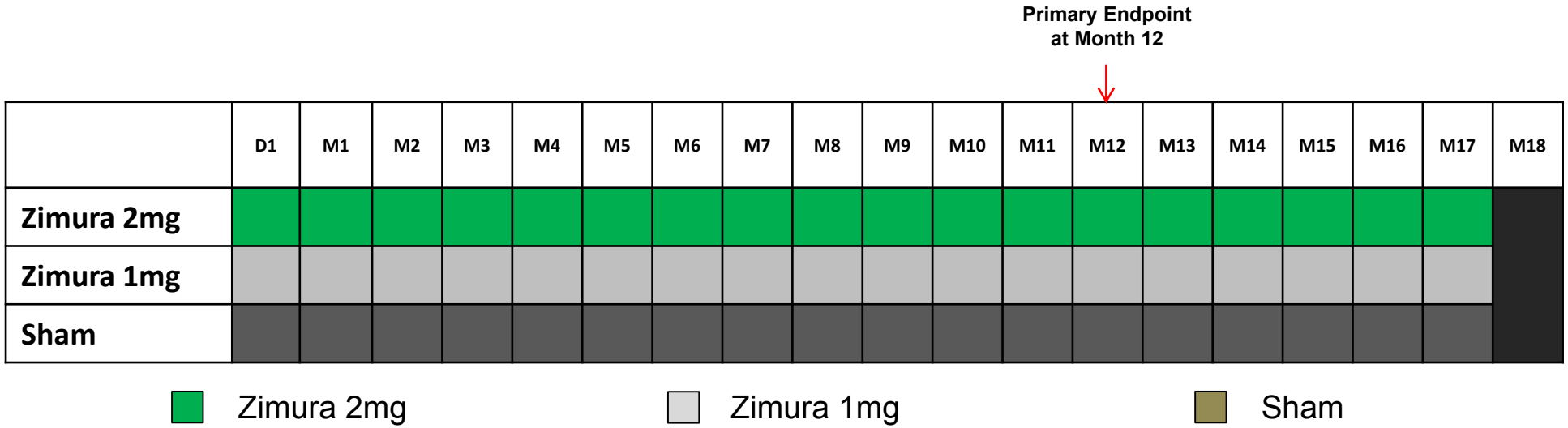


Efficacy Evaluation

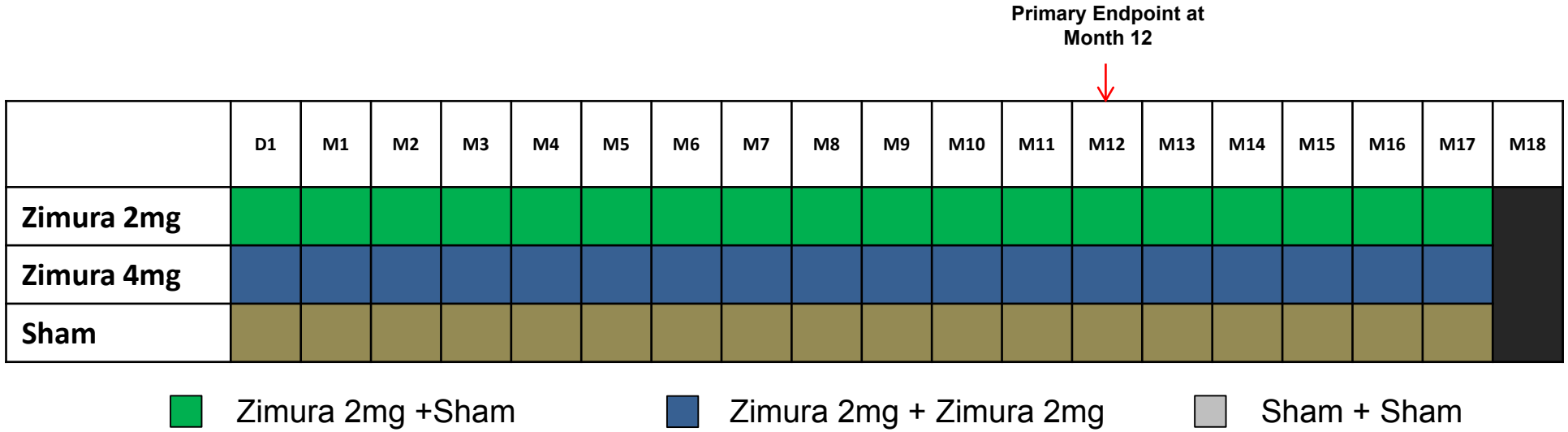
- Zimura 4 mg vs. Sham: based only on subjects randomized in Part 2

Zimura in GA Secondary to Dry AMD Clinical Trial

Part 1:



Part 2:



Key Ophthalmic Inclusion Criteria (Study Eye)

- Non-foveal GA secondary to dry AMD
- Total GA area ≥ 2.5 and ≤ 17.5 mm^2 (1 and 7 disk areas [DA] respectively), determined by screening images of FAF
- If GA is multifocal, at least one focal lesion should measure ≥ 1.25 mm^2 (0.5 DA)
- GA in part within 1500 microns from the foveal center
- The atrophic lesion must be able to be photographed in its entirety
- Best corrected visual acuity in the SE between 20/25 – 20/320, inclusive

Key Ophthalmic Exclusion Criteria

- GA secondary to any condition other than AMD in either eye (e.g., drug-induced)
- Any prior treatment for AMD or any prior intravitreal treatment for any indication in either eye, except oral supplements of vitamins and minerals
- Evidence of CNV in either eye. If CNV develops in the SE during the course of the study, the subject will be withdrawn from the study
- Any ocular condition in the SE that would progress during the course of the study that could affect central vision or otherwise be a confounding factor

Statistical Analysis

- A Mixed -Effects Repeated Measures (MRM) model was used to assess the differences between Zimura 2mg or 4mg dose and their corresponding sham in rate of change of GA area (square root transformation) over 12 months

- The model included the following fixed and *random effects*:
  - Treatment: Sham *vs* dose
  - Study part (1 *vs* 2): only for 2 mg
  - Baseline VA: < 50 letters *vs* ≥ 50 letters
  - Size of baseline GA: < 4 disc area *vs* ≥ 4 disc area
  - Pattern of FAF at the junctional zone of GA: none/focal *vs* banded/diffuse
  - *Visit (0, 6 mos or 12 mos) with unstructured correlation*
  - *Interaction terms between visit and all other factors*

Baseline Characteristics: Generally Balanced Across Cohorts*

	Zimura 2mg N = 67	Sham for 2mg arm N = 110	Zimura 4mg N = 83	Sham for 4mg arm N = 84
Mean Age, Years	78.8	78.2	79.2	78.2
Female Gender, Number (%)	45 (67.2%)	79 (71.8%)	58 (69.9%)	61 (72.6%)
Active smoker, Number (%)	25 (37.3%)	36 (32.7%)	26 (31.3%)	29 (34.5%)
Non-Subfoveal GA, Number (%)	62 (92.5%)	104 (94.5%)	81 (97.6%)	82 (97.6%)
Mean GA Area, mm^2	7.33	7.42	7.90	7.45
Mean SQ Root GA Area, mm	2.62	2.63	2.72	2.64
Bilateral GA, Number (%)	67 (100%)	108 (98.2%)	83 (100%)	83 (98.8%)
Hyper Autofluorescence (%)	66 (98.5%)	109 (99.1%)	82 (98.8%)	83 (98.8%)
Mean BCVA (ETDRS Letters)	70.2	69.0	69.5	68.3
Mean LL BCVA (ETDRS Letters)	36.7	34.5	36.8	33.9
Low Luminance Deficit (BCVA-LL BCVA)	33.5	34.5	32.7	34.4

*Detailed baseline characteristics based on part 1 and part 2 are available online

Preliminary Safety Analysis Through Month 12

- Zimura was generally well tolerated after 12 months of administration
- No Zimura related adverse events
- No Zimura related inflammation
- No drug related discontinuations from the trial attributed to Zimura
- No serious ocular adverse events in the study eye
- No cases of endophthalmitis reported in the clinical trial
- The most frequently reported ocular adverse events were related to the injection procedure
- Incidence of CNV in the untreated fellow eyes was 10 patients (3.5%) and in the study eyes was 3 patients (2.7%) in the sham group, 1 patient (4.0%) in the Zimura 1mg group, 6 patients (9.0%) in the Zimura 2mg group, and 8 patients (9.6%) in the Zimura 4mg group

Primary Efficacy Endpoint Achieved for Both Zimura 2mg and 4mg

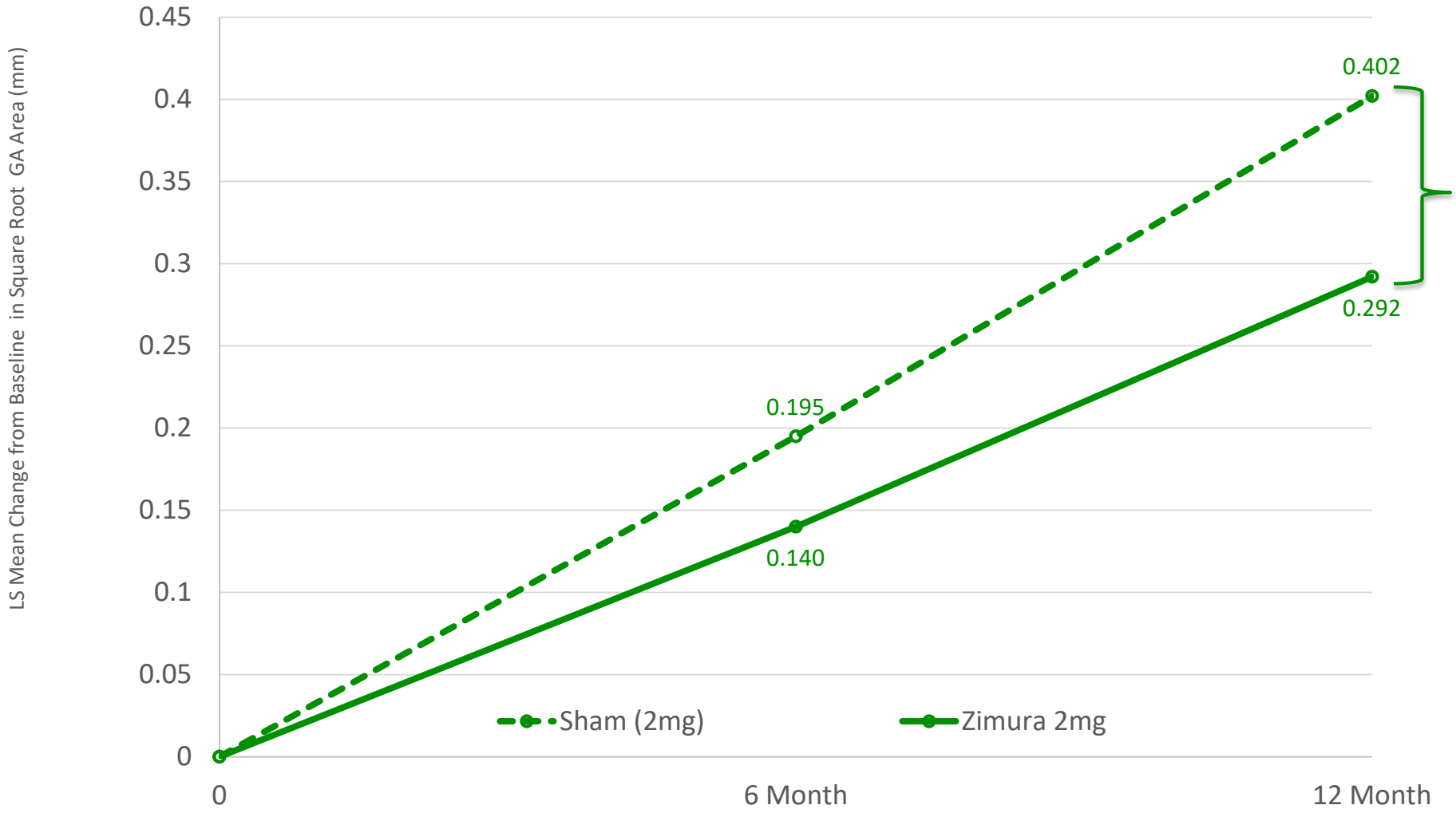
Mean Rate of Change in Geographic Atrophy Area from Baseline to Month 12 (MRM Analysis)
(Square Root Transformation, ITT Population)

Cohort	Zimura 2 mg (N = 67)[c]	Sham 2 mg (N = 110)[c]	Difference	P-value	% Difference
Mean Change in GA[a] (mm)	0.292	0.402	0.110	0.0072[b]	27.38%

Cohort	Zimura 4 mg (N = 83)	Sham 4 mg (N = 84)	Difference	P-value	% Difference
Mean Change in GA[a] (mm)	0.321	0.444	0.124	0.0051[b]	27.81%

(a) = based on the least squared means from the MRM model
(b) = reflects statistically significant p-value; Hochberg procedure was used for significance testing
(c) = 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

Primary Endpoint Achieved: Zimura 2 mg vs. Sham



Based on LSMEANS from MRM Model; ITT Population Hochberg procedure used for significance testing. 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.

Mean Rate of Change in GA for Zimura 2 mg by Part

Mean Rate of Change in Geographic Atrophy (GA) Area from Baseline to Month 12
(MRM Analysis) (Square Root Transformation)

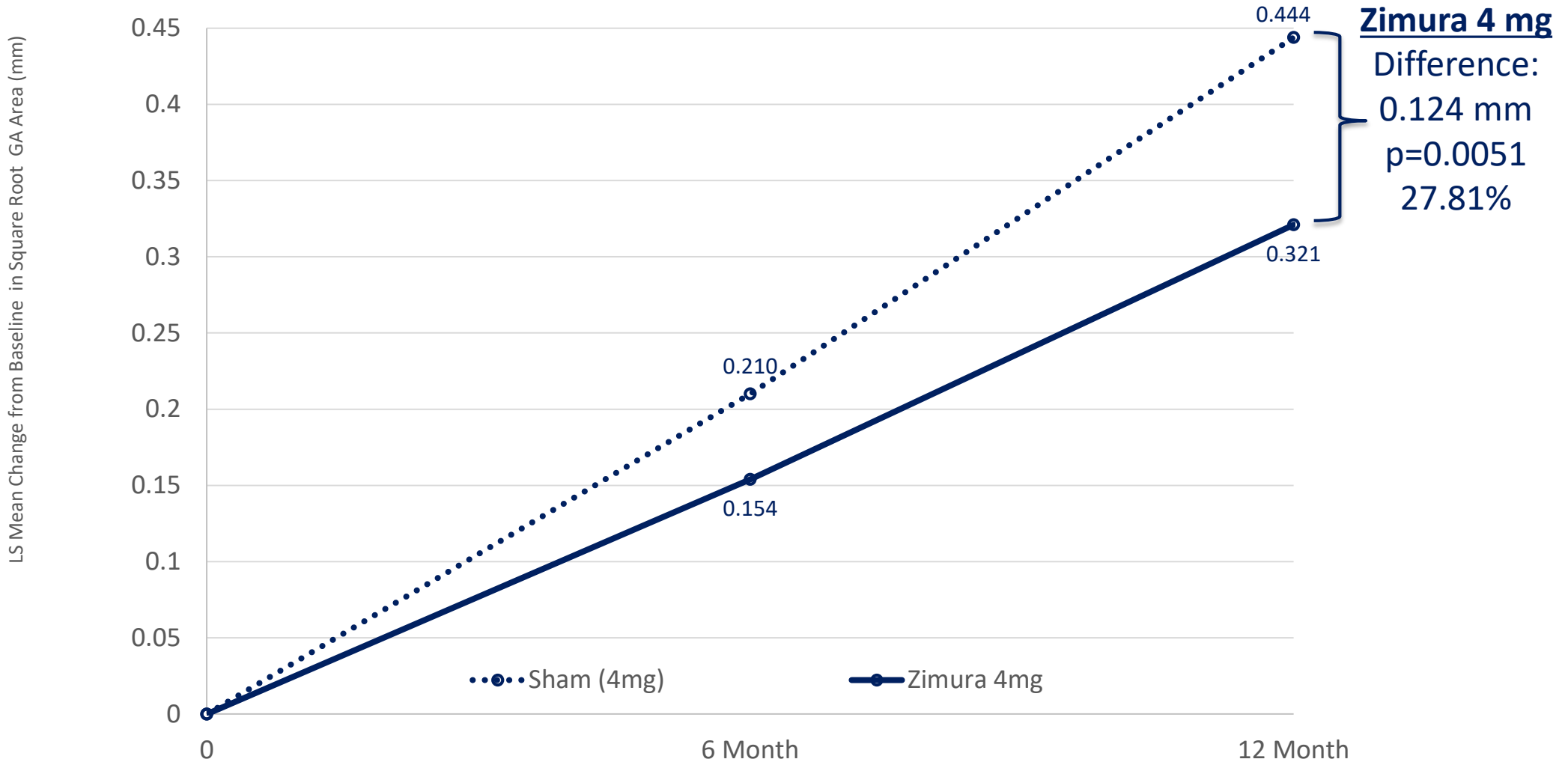
Cohort		Zimura 2mg (N = 25)	Sham 2mg (N = 26)	Difference
Part 1	Mean Change in GA[(a)] (mm)	0.329	0.422	0.093

(a) = based on the least squared means from the MRM model

Cohort		Zimura 2mg (N = 42)	Sham 2mg (N = 84)	Difference
Part 2	Mean Change in GA[(a)] (mm)	0.308	0.422	0.114

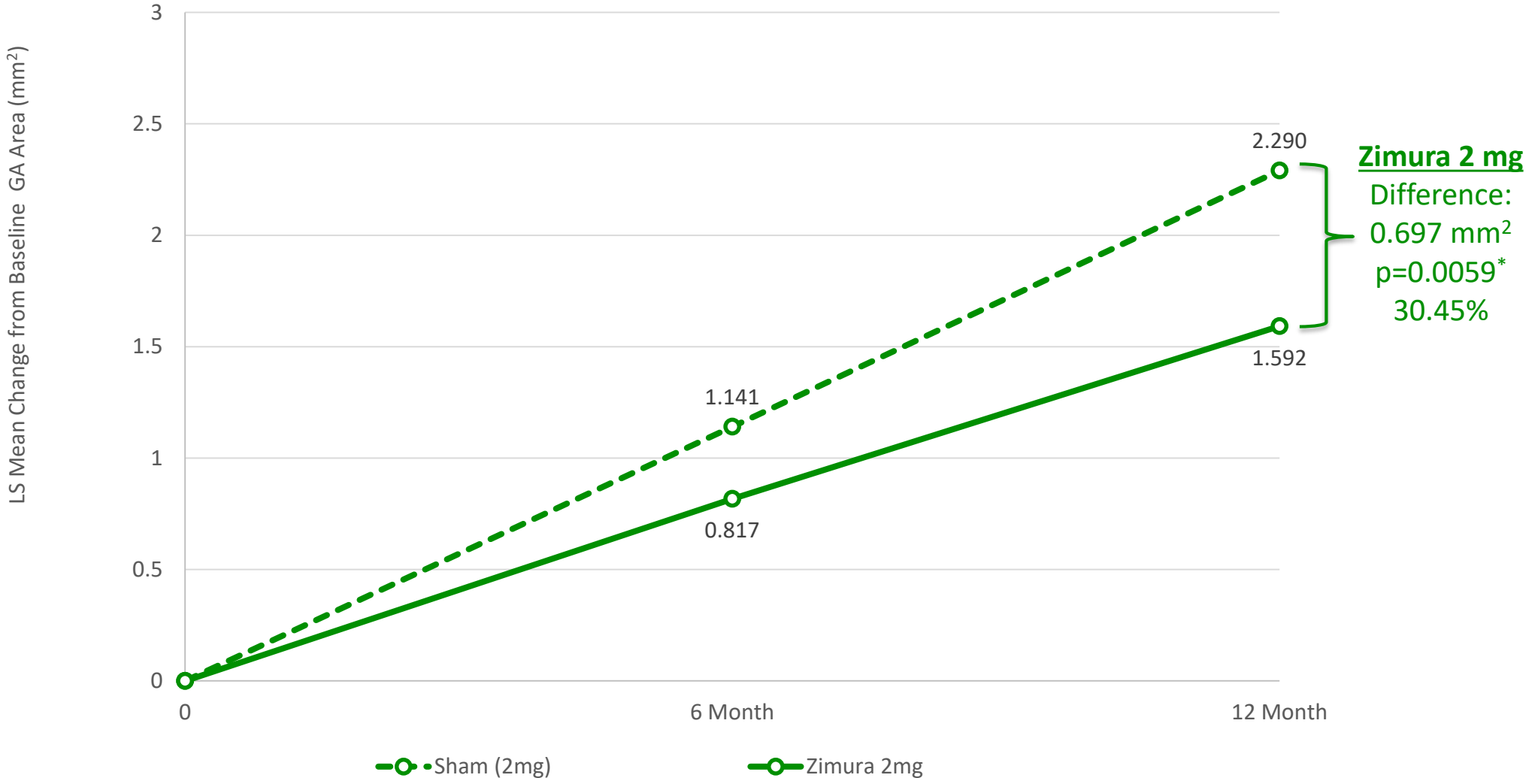
(a) = based on the least squared means from the MRM model

Primary Endpoint Achieved: Zimura 4 mg vs. Sham



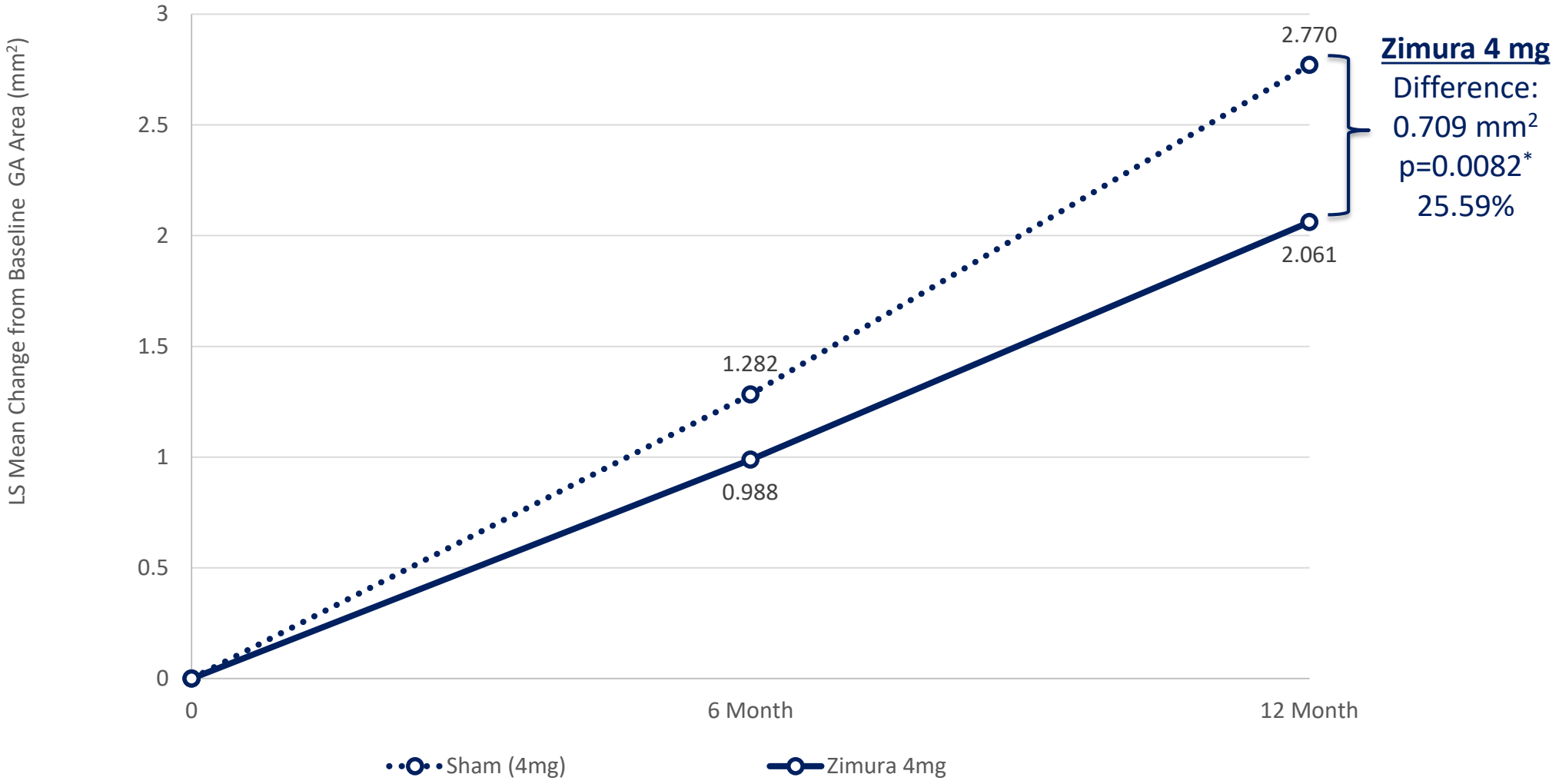
Based on LSMEANS from MRM Model; ITT Population Hochberg procedure used for significance testing

Supportive Efficacy Endpoint: Zimura 2 mg vs. Sham (Non-Square Root)



Based on LSMEANS from MRM Model; ITT Population Hochberg procedure used for significance testing. 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. *Prespecified and descriptive analysis.

Supportive Efficacy Endpoint: Zimura 4 mg vs. Sham (Non-Square Root)



Based on LSMEANS from MRM Model; ITT Population Hochberg procedure used for significance testing. *Prespecified and descriptive analysis.

Secondary Endpoints

- Mean change in best corrected visual acuity (ETDRS letters) from Baseline to Month 12

Cohort	Zimura 2mg (N = 67)	Sham 2mg (N = 110)	Difference
Mean Change in BCVA[a]	-7.90[b]	-9.29[b]	1.39

Cohort	Zimura 4mg (N = 83)	Sham 4mg (N = 84)	Difference
Mean Change in BCVA[a]	-3.79	-3.51	-0.28

- Mean change in low luminance best corrected visual acuity (ETDRS letters) from Baseline to Month 12

Cohort	Zimura 2mg (N = 67)	Sham 2mg (N = 110)	Difference
Mean Change in LL BCVA[a]	-1.03[b]	-1.41[b]	0.38

Cohort	Zimura 4mg (N = 83)	Sham 4mg (N = 84)	Difference
Mean Change in LL BCVA[a]	1.53	2.97	-1.44

(a) = based on the least squared 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

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

Analyzed Geographic Atrophy Data

	N (%) [1]
Missing at baseline[2]	1 (<1%)
Missing at 6 months and at 12 months[2]	36 (14%)
Missing at 6 months only	11 (4%)
Missing at 12 months only	30 (12%)
No missing	182 (70%)
	260 (100%)

[1]Sham, 2mg and 4mg groups

[2]*Excluded from model for 2mg and 4mg*

Sensitivity Analyses

Several pre-specified analyses conducted for primary endpoint:

- Replaced missing data using multiple imputations, with an added “shift” increased until significance is lost
- Replaced missing data by
  - mean value of same treatment arm
  - mean value of opposite treatment arm
  - mean value of both treatment arms
  - mean value of sham arm
- Replaced missing data using “pattern mixture model”
  (useful to investigate “missing not at random” assumptions)

Sensitivity Analyses

Replace missing data using multiple imputations, with an added “shift” increase until significance is lost

Data Imputation Method	Zimura 2mg vs. Sham		Zimura 4mg vs. Sham	
	Difference**	*P*	Difference**	*P*
No imputation (primary analysis)	0.110	0.0072*	0.124	0.0051*
Impute mean value of same arm	0.119	0.0005*	0.152	<0.0001*
Impute mean value of opposite arm	0.075	0.031*	0.107	0.0033*
Impute mean value of both arms	0.097	0.0047*	0.129	0.0003*
Impute mean value of sham arm	**0.093**	**0.0056***	**0.120**	**0.0008***

** Statistically significant (without adjustment for multiplicity)*

*** Difference in means of GA area (square root transformation)*

Sensitivity Analyses

Statistical interpretation:

- All analyses showed small impact of missing data on our overall conclusion on the primary endpoint
- The shift imputation analyses showed that statistical significance would only be lost for large shifts (~40% of observed treatment effect)
- Analysis results were robust to missing data

Conclusions

Zimura Pivotal Trial in geographic Atrophy Secondary to AMD

- Both Zimura 2mg and 4mg were well tolerated over 12 months
- Primary efficacy endpoint was achieved for both Zimura 2mg and Zimura 4mg dose, leading to a ~27% reduction in GA growth over 12 months
- The overall data suggested a dose response relationship
- Initiating the second pivotal clinical trial with the goal of enrolling the first patient in the first quarter of 2020

Initiating Second Pivotal Trial: Planning to Begin Enrolling 1Q 2020

- Our understanding of the regulatory requirements for registration*:
  - **Safety**
    - Rule of 3: To identify adverse events occurring at a rate of 1% or greater:
      - 300 patients exposed to the dose seeking approval (or a higher dose) for a duration of at least 1 year
      - These patients do not need to be only treated for the indication seeking approval
      - A portion of these patients need to be followed for 2 years
  - **Efficacy:** Adequate and well controlled trials
    - Clear statement of the objectives: Slowing down the progression of GA growth
    - Valid Comparison and minimize bias:
      - Two independent randomized, double masked, sham controlled clinical trials
    - Well defined and reliable method of assessment for primary endpoint:
      - Objective endpoint
      - Progression of geographic atrophy over 12 months, measured at 3 timepoints
      - Assessed by an independent and masked reading center
    - Robust statistical analysis to show effect (statistical significance)

*Formal and informal correspondence with regulatory agency
ASRS 2018 Annual Meeting, Vancouver, BC, Presentation by Wiley Chambers, MD

Thank You!

Zimura Pivotal Trial in Geographic Atrophy
Statistical Analysis

Marc Buyse, ScD

Chief Scientific Officer, International Drug Development Institute (IDDI)

Chief Scientific Officer, Clue Points

Associate Professor of Biostatistics

Hasselt University, Belgium

Statistical Take Home Messages

- Statistically significant reductions in GA growth for both 2 mg and 4 mg doses, using mixed effects model
- Little difference in efficacy between 2 mg and 4 mg doses
- Analysis results robust to missing data
- Magnitude of effect may justify independent confirmation in a single additional pivotal trial

Study Design

Part 1: subjects were randomized in a 1:1:1 ratio to

- Zimura 1 mg/eye (N=26)
- Zimura 2 mg/eye (N=25)
- Sham (N=26)

Part 2: subjects were randomized in a 1:2:2 ratio to

- Zimura 2 mg/eye + Sham (N=42)
- Zimura 4 mg/eye (two injections of Zimura 2 mg/eye) (N=83)
- Sham + Sham (N=84)

Analysis by “Intention To Treat”: all randomized patients included

Sample Size

Sample size was calculated so that if the estimated rate of GA growth over 12 months for either 2 mg or 4 mg dose of Zimura *vs.* Sham were

- < 14%, then this dose of Zimura would not be considered to have sufficient efficacy
- ≥ 14% and < 24.5%, then this dose of Zimura would be considered promising enough to be evaluated in a subsequent phase 3 clinical trial
- **≥ 24.5%, then this dose of Zimura would be statistically significantly more effective than Sham**

Primary Analysis – 4 mg

A Mixed-Effects Repeated Measures (MRM) model was used to assess the differences between Zimura 4 mg and Sham in rate of change of GA area (square root transformation) over 12 months

The model included the following fixed and *random effects*:

- Treatment: Zimura 4 mg *vs* Sham
- Baseline VA: < 50 letters *vs* ≥ 50 letters
- Size of baseline GA: < 4 disc area *vs* ≥ 4 disc area
- Pattern of FAF at the junctional zone of GA: none/focal *vs* banded/diffuse
- *Visit (0, 6 mos or 12 mos) with unstructured correlation*
- *Interaction terms between visit and all other factors*

Primary Analysis – 2 mg

Because 2 mg was compared with Sham in both Part 1 and Part 2, a factor was added to the model to adjust for differences between Part 1 and Part 2 (randomization ratios 1:1 and 1:2)

The model included the following fixed and *random effects*:

- Treatment: Zimura 2 mg *vs* Sham
- **Study part: Part 1 *vs* Part 2**
- Baseline VA: < 50 letters *vs* ≥ 50 letters
- Size of baseline GA: < 4 disc area *vs* ≥ 4 disc area
- Pattern of FAF at the junctional zone of GA: none/focal *vs* banded/diffuse
- *Visit (0, 6 mos or 12 mos) with unstructured correlation*
- *Interaction terms between visit and all other factors*

Primary Analysis – "Difference in LS means" 4mg

Square Root of GA	4 mg	Sham	Diff
Difference in LS means*	0.321	0.444	0.124
Overall Relative Difference	**27.81% (*P* = 0.0051)**		

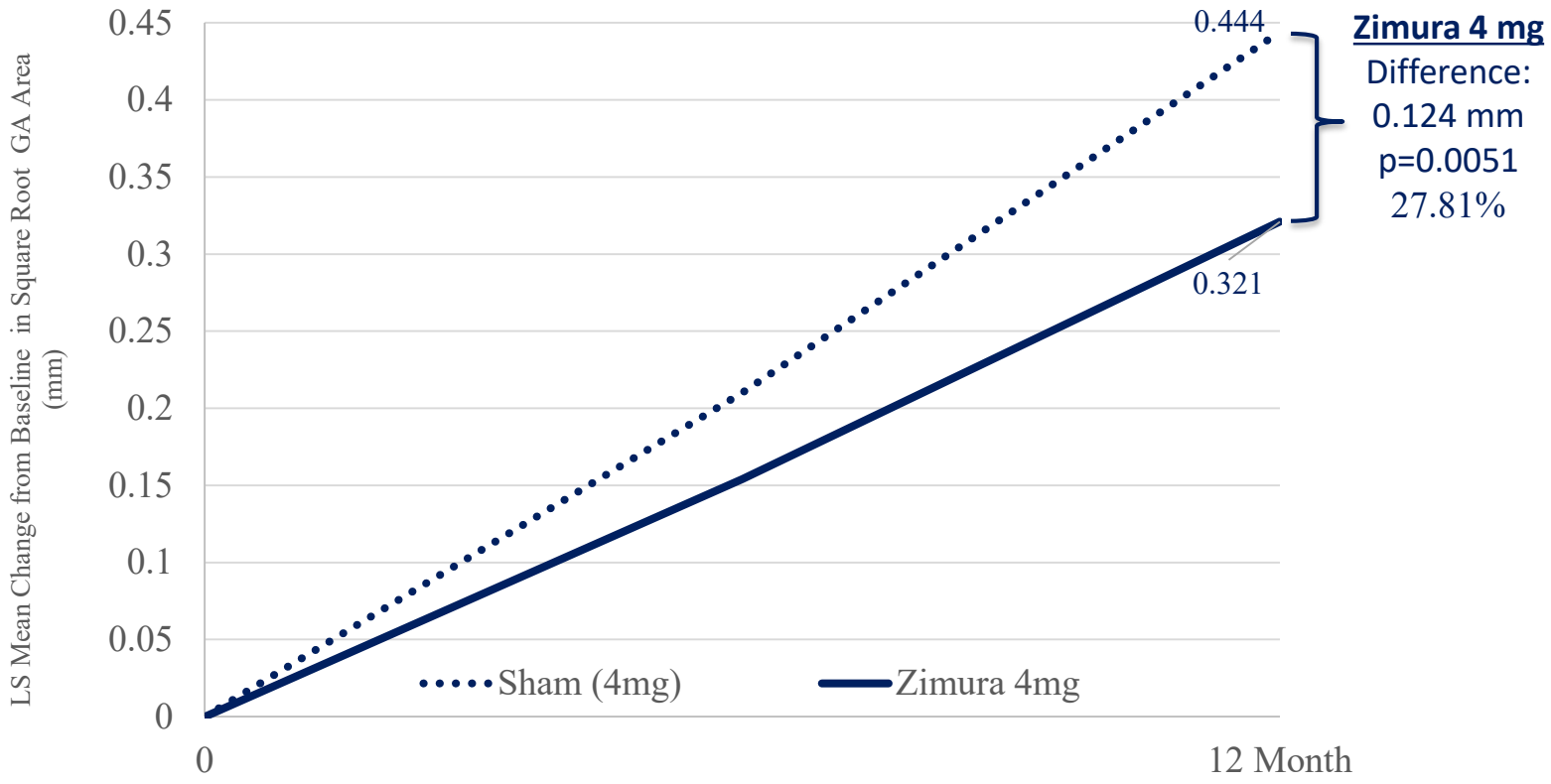
** Model estimated growth rate*

Primary Analysis – "Difference in LS means" 2mg

Square Root of GA	2 mg	Sham	Diff
Part 1 Difference in LS means*	0.329	0.422	0.093
Part 2 Difference in LS means*	0.308	0.422	0.114
Overall Difference in LS means*	0.292	0.402	0.110
Overall Relative Difference	**27.38% (*P* = 0.0072)**		

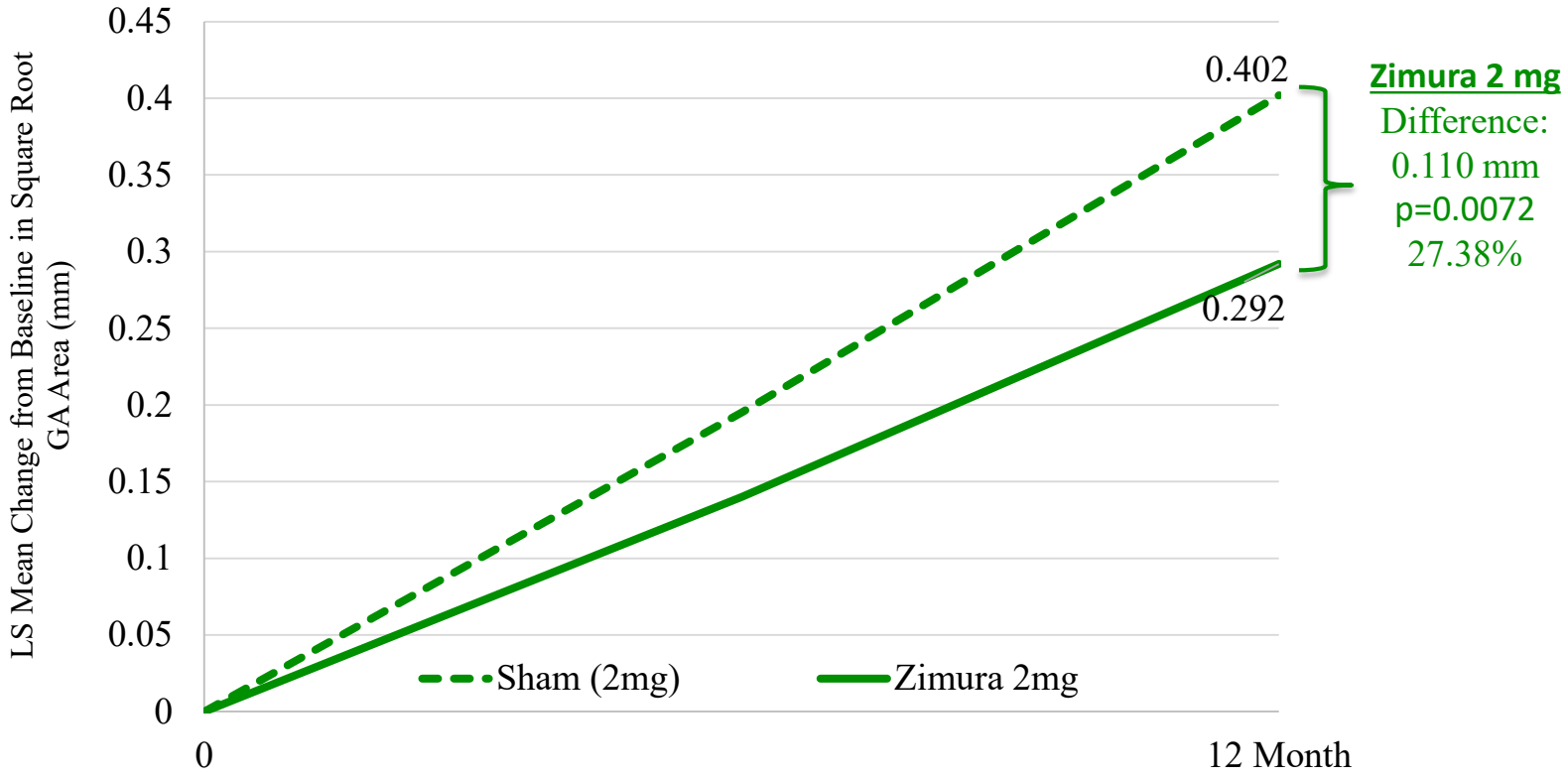
** Model estimated growth rate*

Primary Endpoint Achieved: Zimura 4 mg *vs* Sham



Based on LSMEANS from MRM Model; ITT Population Hochberg procedure used for significance testing

Primary Endpoint Achieved: Zimura 2 mg *vs* Sham



Based on LSMEANS from MRM Model: ITT Population Hochberg procedure used for significance testing

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.

Primary Analysis

Statistical interpretation:

- Treatment effects are estimated from model that adjusts for baseline covariates, study part, and missing data
- Benefits of similar magnitude and equally robust for the two doses of Zimura (~27% reduction in GA growth)
- Benefits comfortably significant
- Proportional benefits from baseline to 6 months, and from 6 to 12 months

Missingness of Geographic Atrophy Data

	N (%)[1]
Missing at baseline[2]	1 (<1%)
Missing at 6 months and at 12 months[2]	36 (14%)
Missing at 6 months only	11 (4%)
Missing at 12 months only	30 (12%)
No missing	182 (70%)
	260 (100%)

[1]Sham, 2mg and 4mg groups
[2]*Excluded from model for 2mg and 4mg*

Sensitivity to Missing GA Data

Several pre-specified analyses conducted per FDA conventions:

1. Replaced missing data by
   - mean value of same treatment arm
   - mean value of opposite treatment arm
   - mean value of both treatment arms
   - mean value of sham arm
2. Replaced missing data using multiple imputation, with an added «shift» (shift increased until significance was lost)
3. Replaced missing data using «pattern mixture model» (useful to investigate «missing not at random» assumptions)

Sensitivity to Missing GA Data (4 mg)

Data imputation method	Difference**	*P*
No imputation (primary analysis)	0.124	0.0051*
Impute mean value of same arm	0.152	<0.0001*
Impute mean value of opposite arm	0.107	0.0033*
Impute mean value of both arms	0.129	0.0003*
Impute mean value of sham arm	**0.120**	**0.0008***

** Statistically significant (without adjustment for multiplicity)*
*** Difference in means of GA area (square root transformation)*

Sensitivity to Missing GA Data (2 mg)

Data imputation method	Difference**	*P*
No imputation (primary analysis)	0.110	0.0072*
Impute mean value of same arm	0.119	0.0005*
Impute mean value of opposite arm	0.075	0.031*
Impute mean value of both arms	0.097	0.0047*
Impute mean value of sham arm	**0.093**	**0.0056***

** Statistically significant (without adjustment for multiplicity)*

*** Difference in means of GA area (square root transformation)*

Sensitivity to Missing GA Data

Statistical interpretation:

- Missing data were as expected in this indication
- All analyses showed small impact of missing data
- The shift imputation analyses showed that statistical significance would only be lost for large shifts
- **Analysis results were robust to missing data**

Statistical Take Home Messages

- Statistically significant reductions in GA growth for both 2 mg and 4 mg doses, using mixed effects model
- Little difference in efficacy between 2 mg and 4 mg doses
- Analysis results robust to missing data
- Magnitude of effect may justify independent confirmation in a single additional pivotal trial

Thank You

Regulatory Endpoint for Geographic Atrophy

Karl G. Csaky, M.D., Ph.D.
T. Boone Pickens Senior Scientist
Director of the Molecular Ophthalmology Laboratory
Clinical Center of Innovation for Age-Related Macular Degeneration
Retina Foundation of the Southwest

Take Home Message

- Geographic atrophy expansion – loss of retinal tissue
- Loss of retinal tissue – profound effects on patient's "total" vision and quality of life
- Drugs that can reduce geographic atrophy expansion: Large impact on patient's activity of daily living
- **FDA considers a reduction in geographic atrophy expansion – approval endpoint – with a strong consideration of the safety of the drug**

Geographic Atrophy (GA)

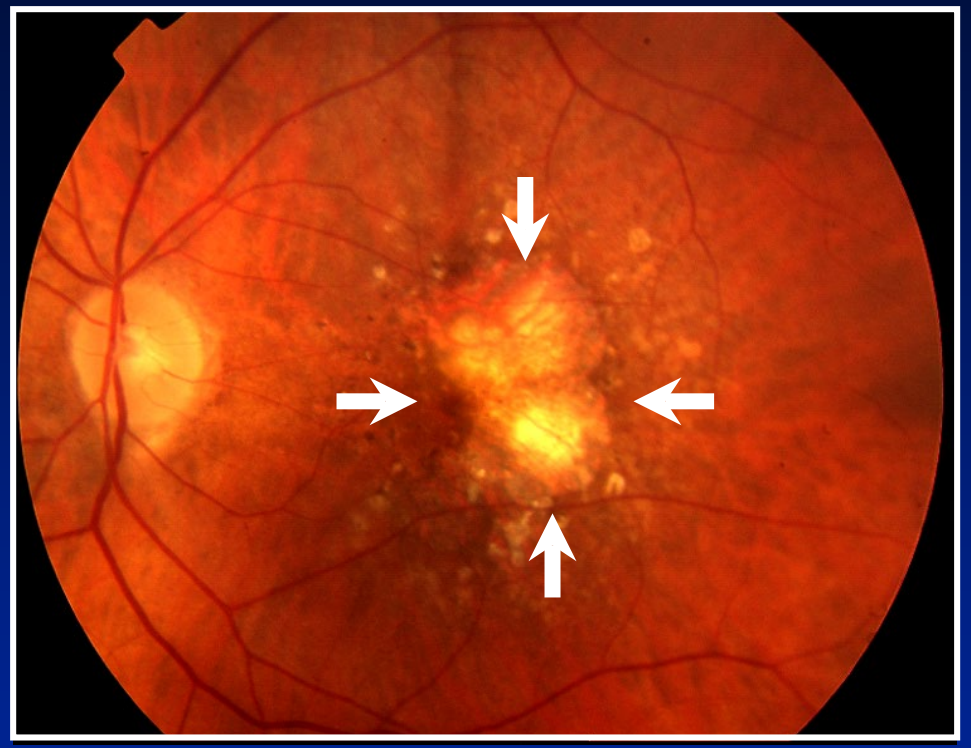
- GA is characterized by atrophic patches and focal hypopigmentation[1,2]
  - Atrophic patches are focal areas that lack RPE, photoreceptors, and choriocapillaris[1]
  - Large choroidal vessels may be visible through the atrophic patches[1]
  - Focal hypopigmentation involves thinning of the RPE and reduced melanin density[2]

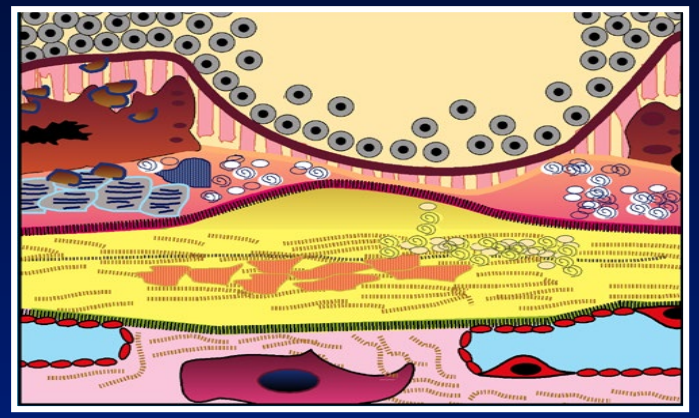
Atrophic Area of RPE; Choroidal Vessels Are Visible

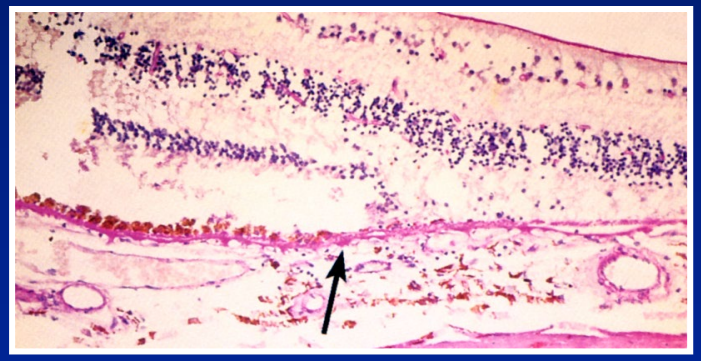
1. Rosenfeld PJ *et al*. In: Yanoff M, Duker JS. *Ophthalmology* 3rd ed. 2009; Elsevier Inc.
2. Holz FG, Pauleikhoff D. In: Holz FG *et al*. Age-related macular degeneration. 2004; Springer-Verlag.

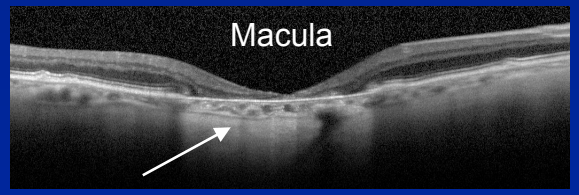
Geographic Atrophy

Degenerative atrophy of the RPE and photoreceptors

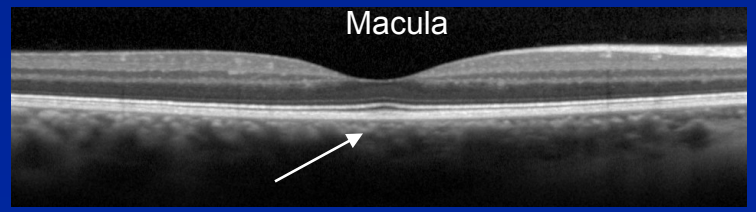








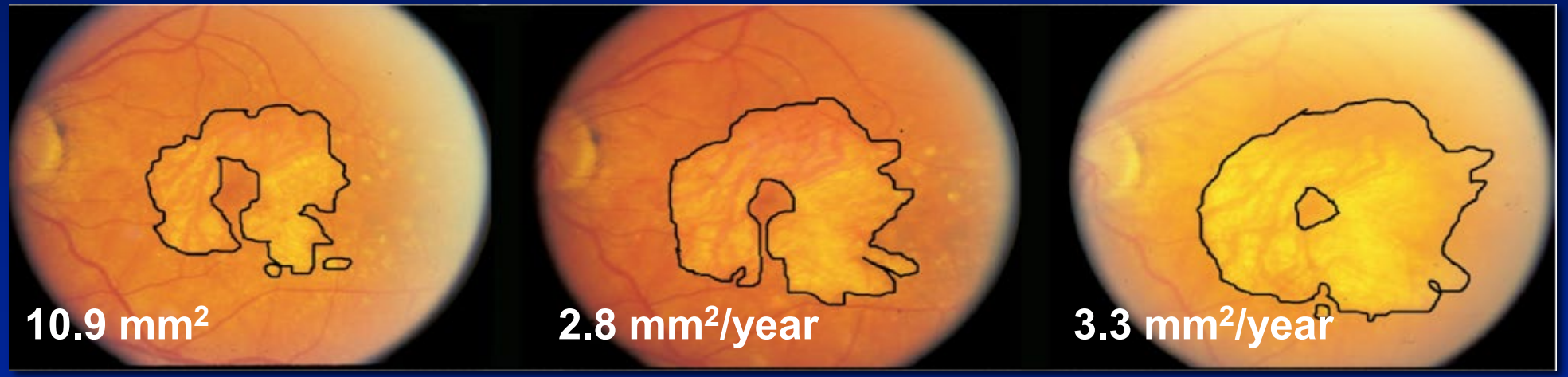
Geographic Atrophy



Normal

Geography Atrophy Progression

Baseline	≈2 Years	4 Years



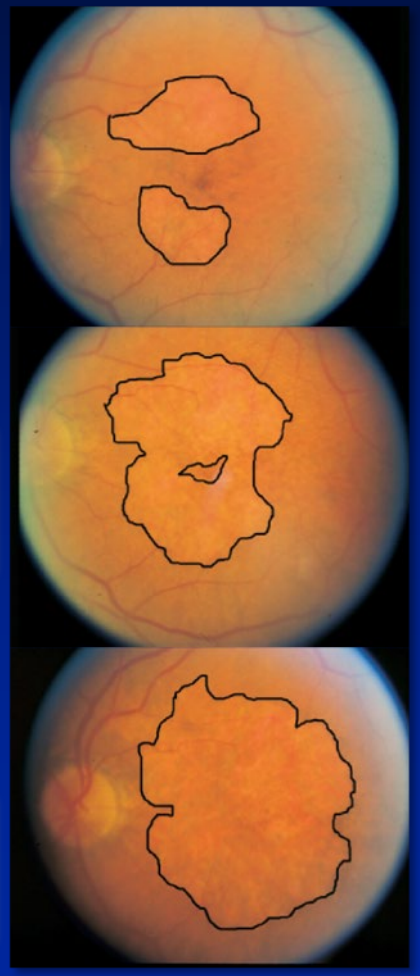
1. Sunness et al. *Ophthalmology*. 2007;114(2):271.

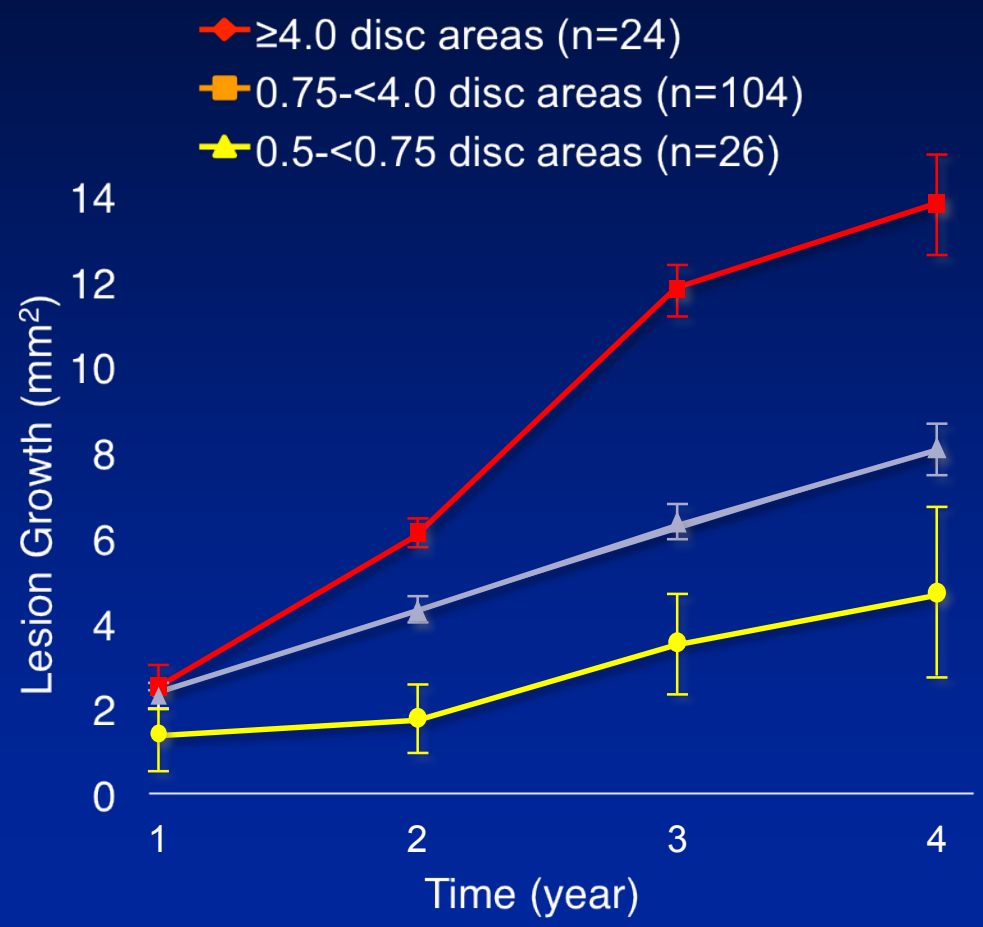
CFP Can be Used to Measure GA Lesion Size and Predict Lesion Growth[1,2]

Baseline
8.9 mm^2

2.2 years
6.1 mm^2/year for the first 2 years

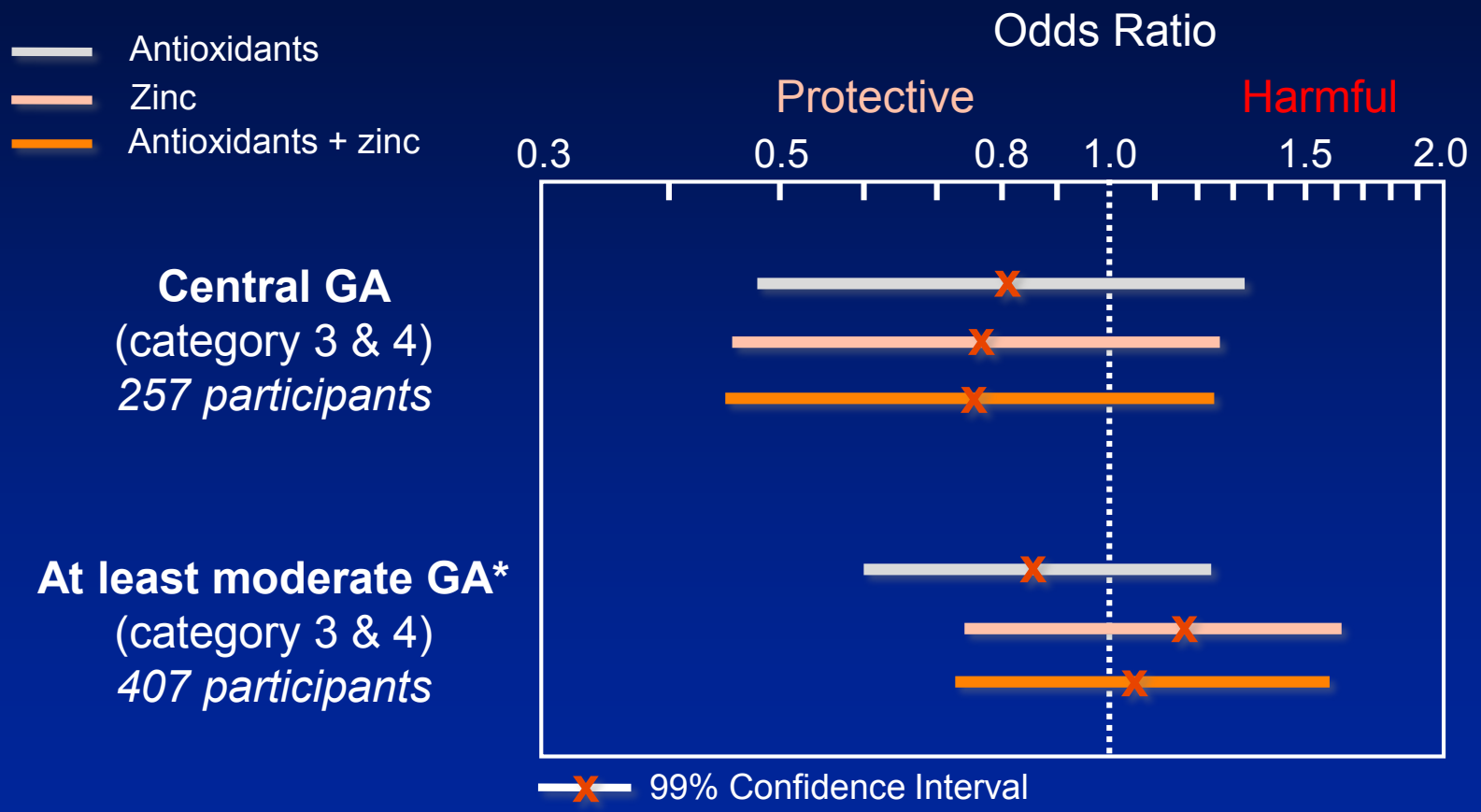
4.3 years
4.6 mm^2/year for the second 2 years





1. Sunness et al. *Ophthalmology*. 2007;114(2):271. 2. Lindblad et al. *Arch Ophthalmol.* 2009;127(9):1168.

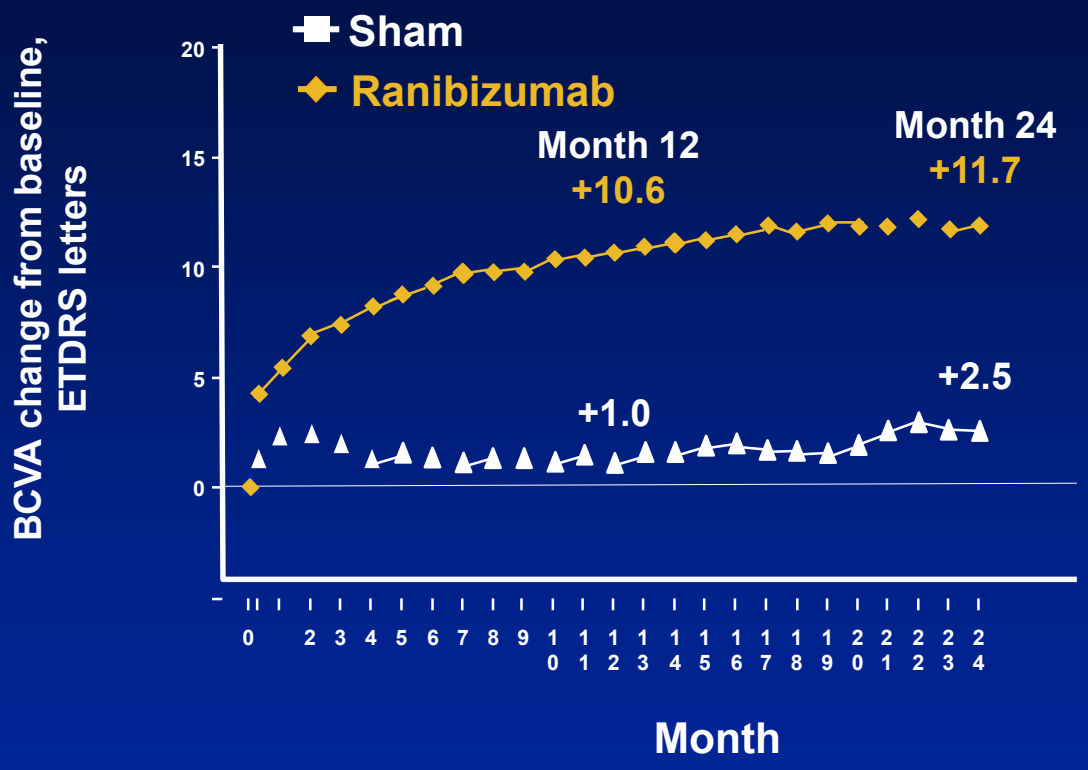
Antioxidants and/or Zinc Confer no Significant Benefit for the Onset or Progression of GA[1,2]



*>360 µm not necessarily involving the center of the macula

1. Age-Related Eye Disease Study Research Group. *Arch Ophthalmol*. 2001;119(10):1417. **2.** Lindblad et al. *Arch Ophthalmol*. 2009;127(9):1168.

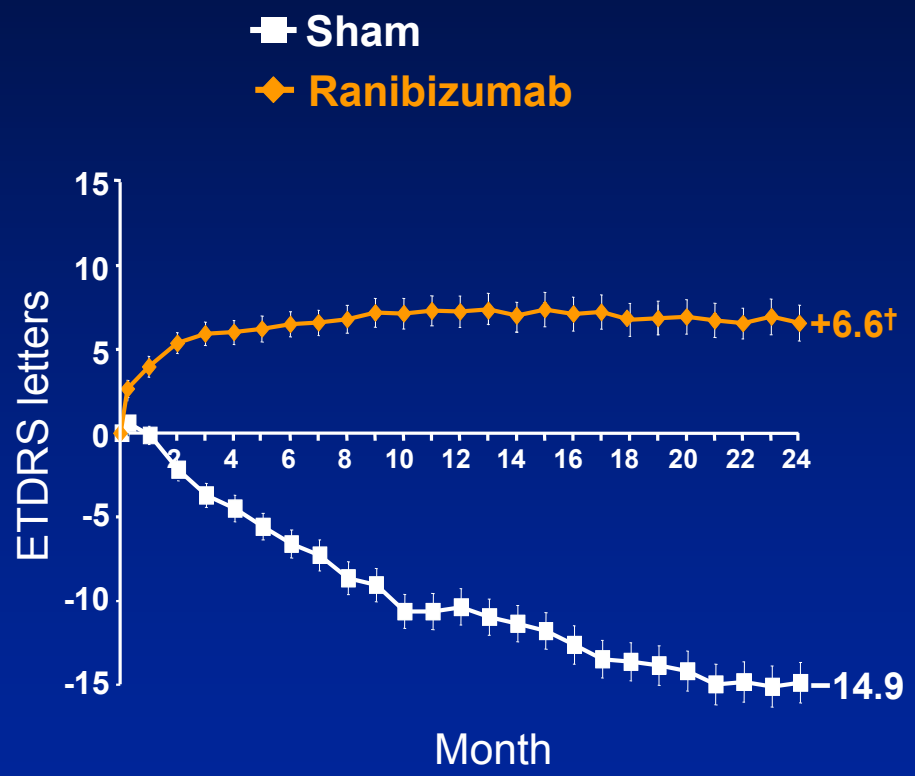
Ranibizumab Approval for Diabetic Macular Edema and Neovascular Age-Related Macular Degeneration - Mean Change in Vision Over Time



9.2-letter difference compared with **sham**

P<0.01

RIDE/RISE[2]



†21.1-letter difference compared with **sham**

P<0.01

MARINA[1]

1. Rosenfeld et al. *N Engl J Med.* 2006;355:1419. 2. Nguyen et al. *Ophthalmology* 2012;119;789

Vision Loss a Poor Predictor of Disease Progression in Geographic Atrophy

Change in Area of Geographic Atrophy in the Age-Related Eye Disease Study

Arch Ophthalmol. 2009;127(9):1168-1174

443 subjects developed central GA during the course of the study; of these 155 were Followed for 5 years

Over 5 years mean visual acuity decreased ~4 letters per year

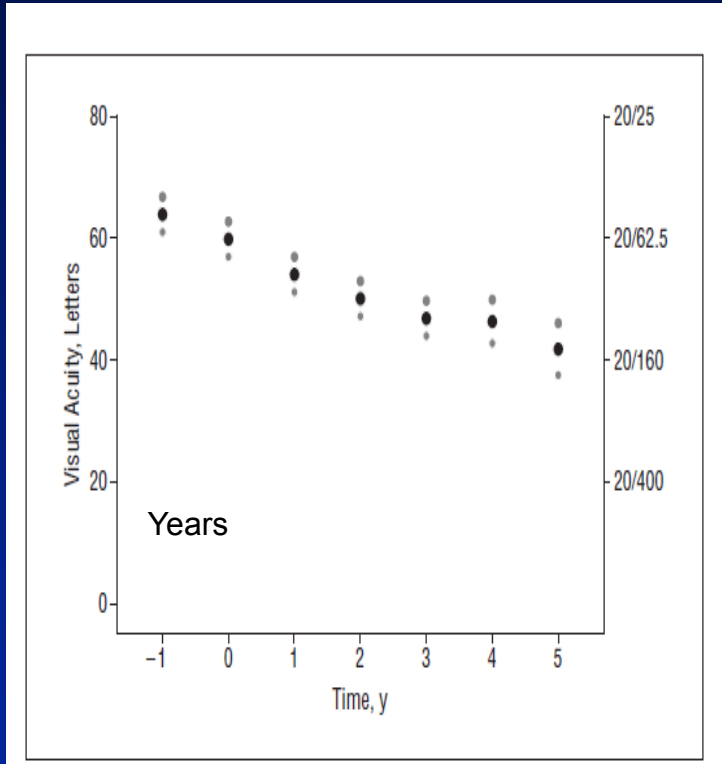


Figure 5. Mean visual acuity over time following development of central geographic atrophy. The small dots indicate 95% confidence intervals.

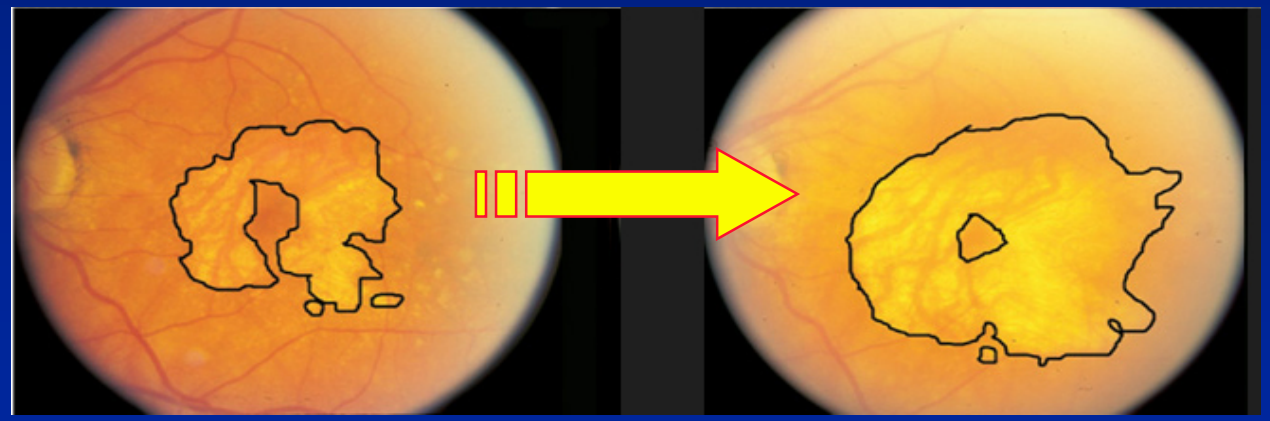
RESEARCH OPPORTUNITIES

Report from the NEI/FDA Ophthalmic Clinical Trial Design and Endpoints Symposium*

Karl G. Csaky,[1] *Elaine A. Richman,*[2] *and Frederick L. Ferris, III*[3]

Invest Ophthalmol Vis Sci: 49: 479 (2008)

Reducing the Increase in the Size of Geographic Atrophy is an Acceptable Endpoint for Approval



Ophthalmology. 114: 271 (2007)

Fundus Autofluorescence Imaging

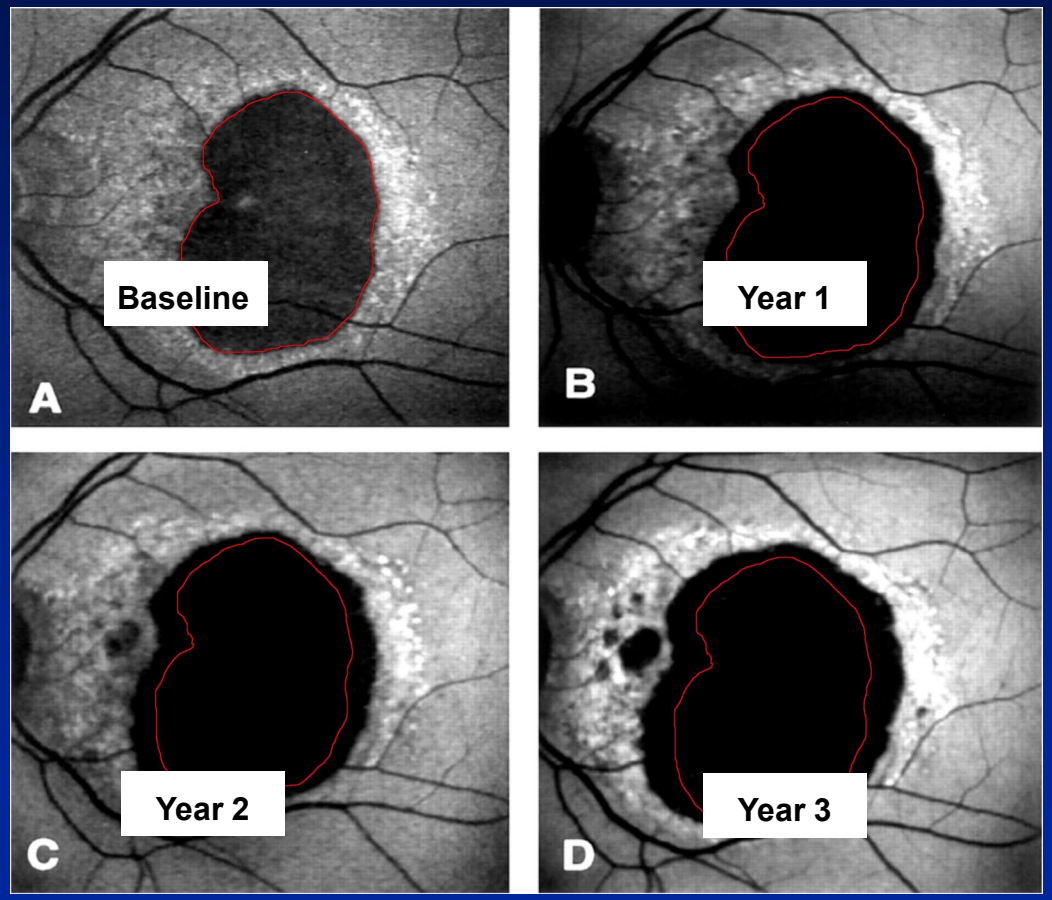
- Acquiring Images with cSLO (HRA2 Heidelberg, Germany)
- Excitation at 488 nm: optically pumped solid-state laser Emission is detected above 500 nm with a barrier filter
- 30˚ x 30˚ FAF image: encompasses macular area
- Mean image is generated to amplify the FAF signal

Single Image

Mean Image

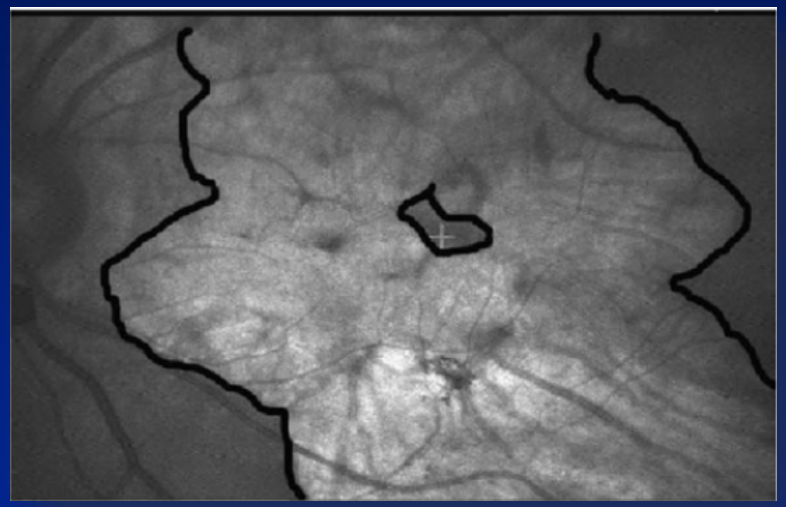
Increase in Geography Atrophy Size over Time as Detected by Fundus Autofluorescence

Objective Approach to Measure Loss of Retinal Tissue

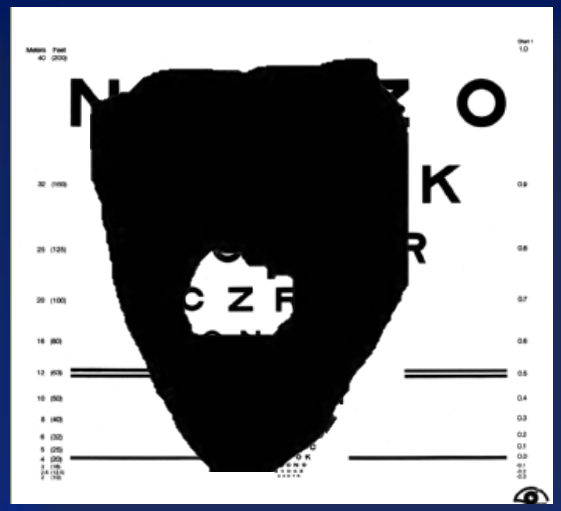


Original Size =

GA lesions Are Often Foveal-sparing and Impact Visual Function Beyond VA[1,2] Therefore GA Patients Can Have Profound Vision Deficits Even With Good VA[3]



Foveal-Sparing Lesion



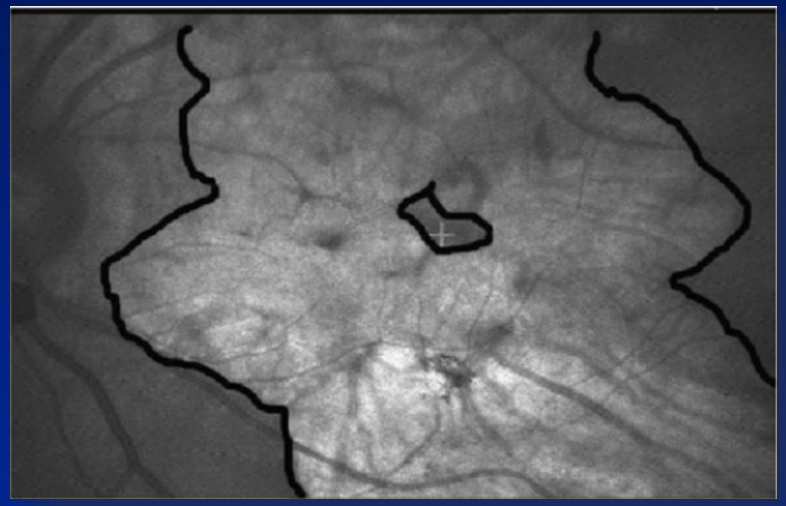
VA 20/50*

Driving Sign

1. Sunness et al. *J Vis Impair Blind*. 2008;102(10):600. **2.** Sunness. *J Vis Impair Blind*. 2008;102(11):679.

3. Sunness et al. *Ophthalmology*. 2007;114(2):271.

GA Lesions Slowing Expand: – 25% Change – Implications for Patients



Foveal-Sparing Lesion

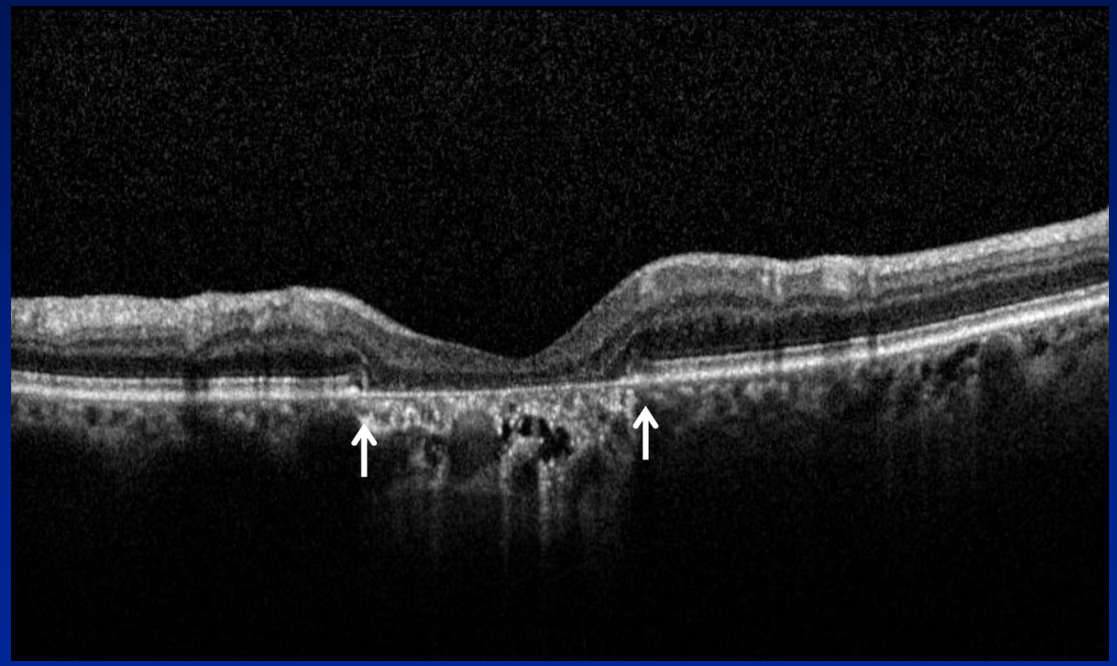
Research Opportunities

Report From the NEI/FDA Endpoints Workshop on Age-Related Macular Degeneration and Inherited Retinal Diseases

Karl Csaky,[1] *Frederick Ferris III*,[2] *Emily Y. Chew*,[2] *Prashant Nair*,[3] *Janet K. Cheetham*,[4] *and Jacque L. Duncan*[5]

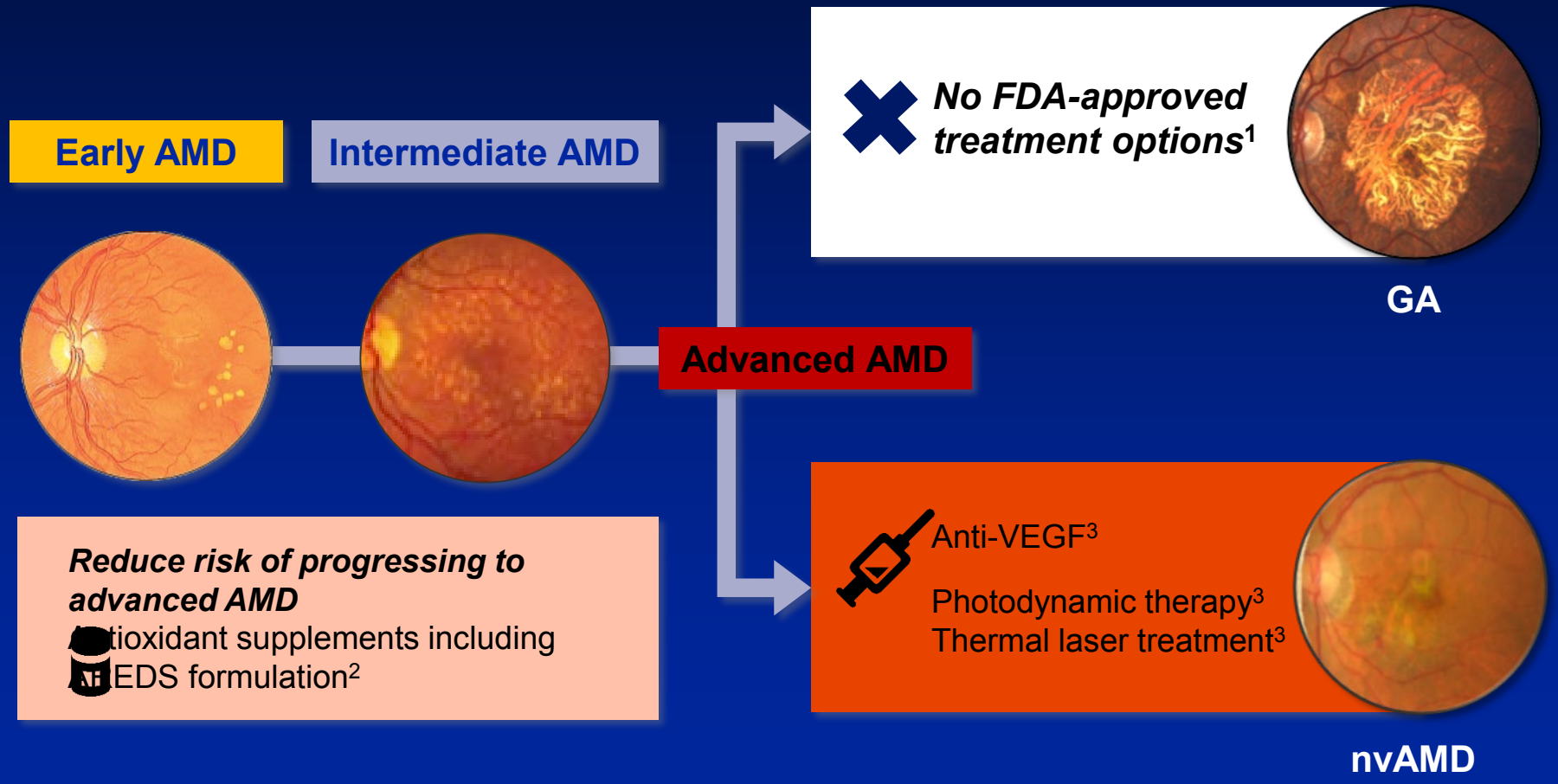
Invest Ophthalmol Vis Sci: 58: 3456 (2017)

Close Correlation of Size of the Atrophy in FAF Images With Photoreceptor Loss on SD-OCT



Schmitz-Valckenberg S IOVS 2011; 52:1.

There Are No FDA-Approved Treatment Options for GA



1. Holz et al. *Ophthalmology*. 2014;121(5):1079. **2.** Evans and Lawrenson. *Cochrane Database Syst Rev*. 2012;11:CD000254. **3.** http://www.nei.nih.gov/health/maculardegen/armd_facts.asp. Accessed 4 May, 2015.

FDA Review:

- The United States Federal Food, Drug, and Cosmetic Act is a set of laws passed by Congress in 1938 - oversee the safety of food, drugs, medical devices, and cosmetics

- 1962 Kefauver-Harris Amendment - requirement that all new drug applications demonstrate "substantial evidence" of the drug's efficacy for a marketed indication

Take Home Message

- Geographic atrophy expansion – loss of retinal tissue
- Loss of retinal tissue – profound effects on patient's "total" vision and quality of life
- Drugs that can reduce geographic atrophy expansion: Large impact on patient's activity of daily living
- **FDA considers a reduction in geographic atrophy expansion – approval endpoint – with a strong consideration of the safety of the drug**

Zimura Pivotal Trial: Imaging Analysis

Glenn Jaffe, MD

Director, Duke Reading Center

Robert Machemer Professor of Ophthalmology

Chief, Retina Division

Duke Eye **Center**

Take-home Message

Robust, rigorous grading methodology gives confidence in study endpoint data

Duke Reading Center : Overview

- Established 2001
- Experienced staff consisting of physicians and other experts in imaging/functional testing
- Multiple Publications
- Image research/development
- Varied clinical trials
- Over 17,000 US and ROW OCT Technicians and Photographers certified
- Phase I-IV studies
- Single site-multicenter global
- 10-2400 subjects

Our Experience-Diseases

- Retinal vascular (DME/RVO/DR)
- NVAMD
- Intermediate AMD
- **GA**
- Hereditary retinal degeneration
- RD
- Vitreous pharmacolysis
- Uveitis
- Glaucoma
- Optic neuritis/MS
- Non-ophthalmic safety studies

Our Experience-Diseases

- Retinal vascular (DME/RVO/DR)
- NVAMD
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- **GA**
- Hereditary retinal degeneration
- RD
- Vitreous pharmacolysis
- Uveitis
- Glaucoma
- Optic neuritis/MS
- Non-ophthalmic safety studies

Our Imaging Experience Relevant to Zimura GA Trial

- Extensive AMD study experience (Dry and Wet)
- **35 treatment trials for AMD (10 GA trials)**
- **Largest AMD trials to-date (CATT, VIEW 1, HAWK etc)**
- Have led to drug registration (US, Ex-US)
- Provide consultation to sponsors
- Develop appropriate grading variables
- Safety reporting system

Our Imaging Experience Relevant to Zimura GA Trial

- Image based eligibility
  - Optical Coherence Tomography (OCT)
  - Infrared imaging (IR)
  - Fluorescein angiography (FA)
  - Fundus autofluorescence (FAF)
  - Color fundus photography
- Image-based endpoints FAF/OCT/IR
- Image-based safety OCT/IR

Reader Experience

- 3 primary Readers during study
- All three Senior Readers
- Each more than 10 years experience
- Excellent Reader Agreement

Director of Grading Experience

- Founder and Director of DRC
- 30 years clinical trial experience (site PI, Individual IND)
- Basic science program-complement role in AMD
- Director of Grading for DRC AMD trials
- Member of CAM
- Director of Duke Dry AMD meeting

Many Relevant DRC Publications

- CAM
- AMD reader reproducibility
- Novel AMD image interpretation methods
- AMD/complement basic science

Zimura Pivotal Trial: Robust Grading Methodology

Rigorous Review Process

- Completely masked assessment
- Each visit evaluated independently
- 2 experienced 1^0 Readers measure GA lesion size on FAF with RegionFinder
- Discrepancies >10% arbitrated
- Arbitrator is Glenn Jaffe, MD, Director of Grading
- lesions measured on FAF with OCT and NIR used as supportive modalities

GA Defined on OCT by cRORA

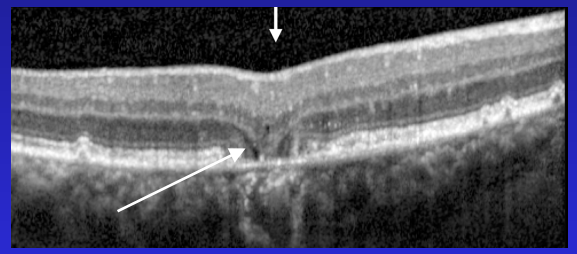
Ophthalmology. 2017 Nov 2. pii: S0161-6420(17)31703-7. doi: 10.1016/j.ophtha.2017.09.028. [Epub ahead of print]

Consensus Definition for Atrophy Associated with Age-Related Macular Degeneration on OCT: Classification of Atrophy Report 3.

Sadda SR[1], Guymer R[2], Holz FG[3], Schmitz-Valckenberg S[3], Curcio CA[4], Bird AC[5], Blodi BA[6], Bottoni F[7], Chakravarthy U[8], Chew EY[9], Csaky K[10], Danis RP[6], Fleckenstein M[3], Freund KB[11], Grunwald J[12], Hoyng CB[13], Jaffe GJ[14], Liakopoulos S[15], Monés JM[16], Pauleikhoff D[17], Rosenfeld PJ[18], Sarraf D[19], Spaide RF[10], Tadayoni R[20], Tufail A[21], Wolf S[22], Staurenghi G[7].

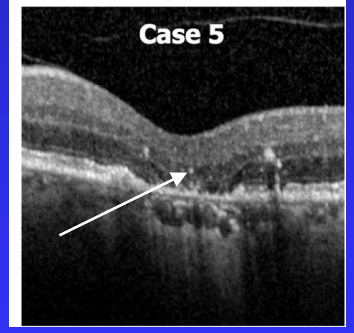
- Outer retinal layer (photoreceptor) loss
- RPE loss
- Choroidal hypertransmission
- >250u lesion

cRORA Examples



Photoreceptor loss due to GA

cRORA



We used CAM Criteria in This Trial!

Primary Efficacy Endpoint

Mean rate of change in GA over 12 months measured by fundus autofluorescence (FAF) at three time points: Baseline, Month 6, and Month 12

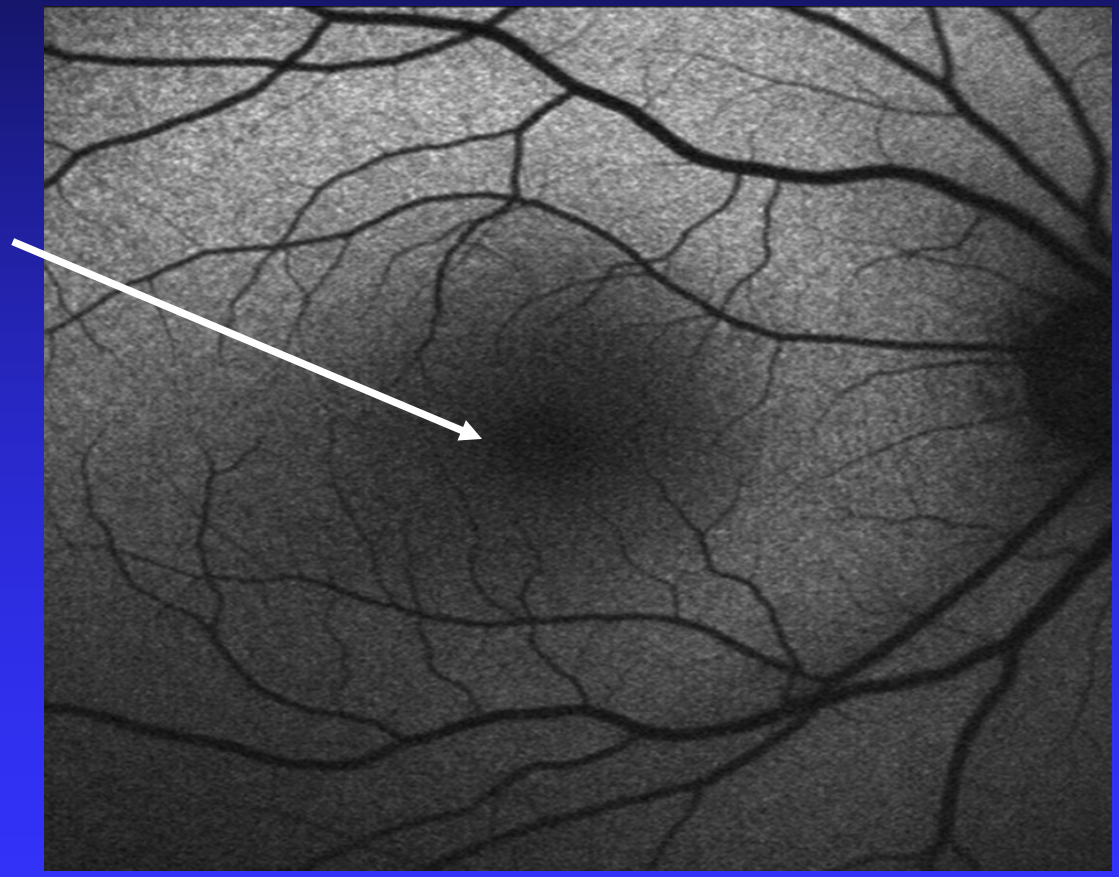
GA Endpoint

- Objective, more reproducible than VA
- FDA recognizes tis objective endpoint
- Reflects function
- GA causes blind spot
- Functionally very important to patient!

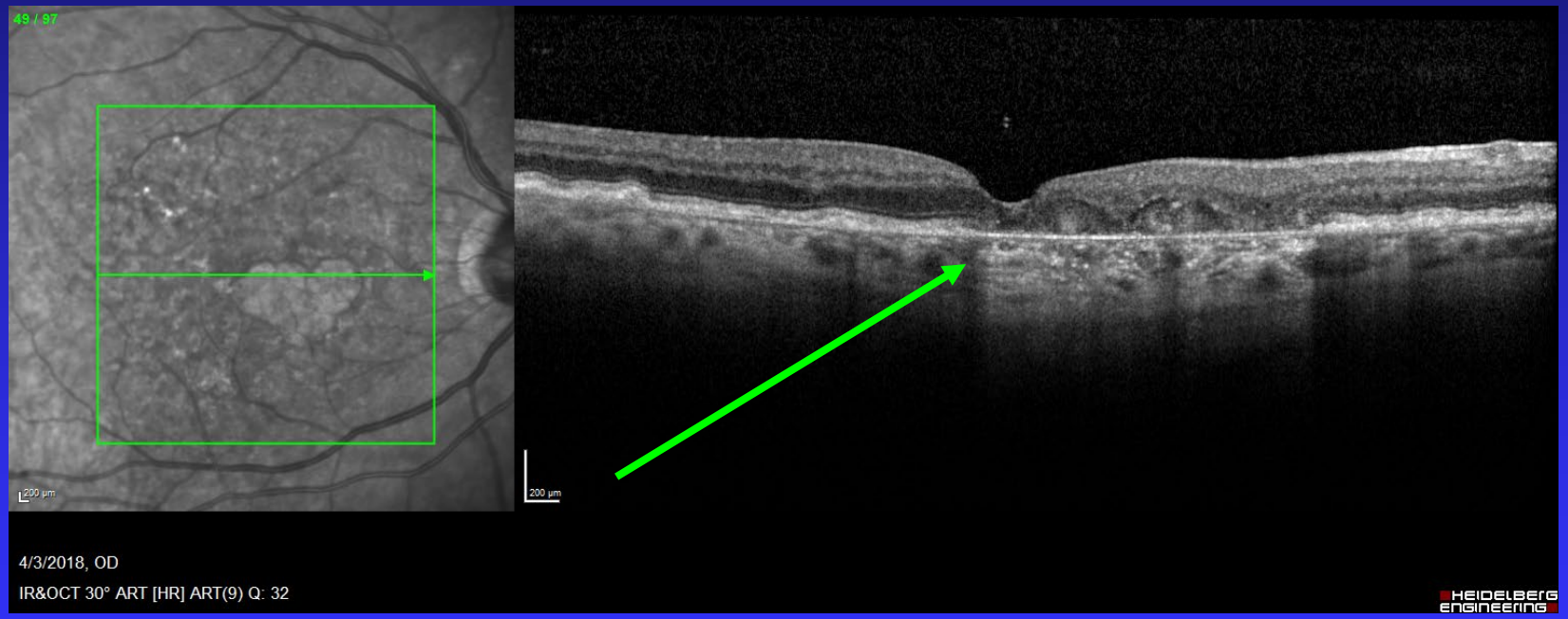
Normal FAF

Blue Light FAF

Need to distinguish normal from pathologic FAF



Fovea Involving?



Not eligible-OCT helpful!

NIR Helps Identify GA Boundaries

RegionFinder Measurement

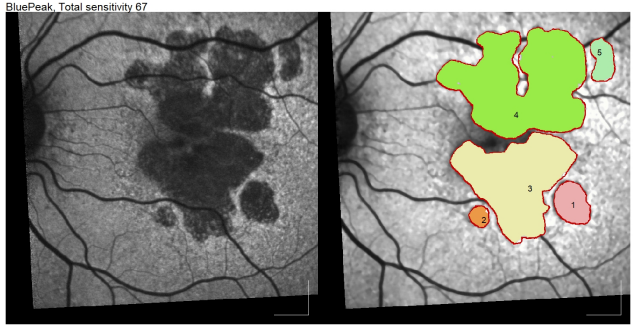
SPECTRALIS® RegionFinder
Single Exam Report

HEIDELBERG ENGINEERING

Patient:		**DOB:**	1/1/2001	**Sex:**	F
Patient ID:		**Exam.:**	6/10/2019		
Diagnosis:		**Comment:**			

OS

BluePeak, Total sensitivity 67



Reading Details

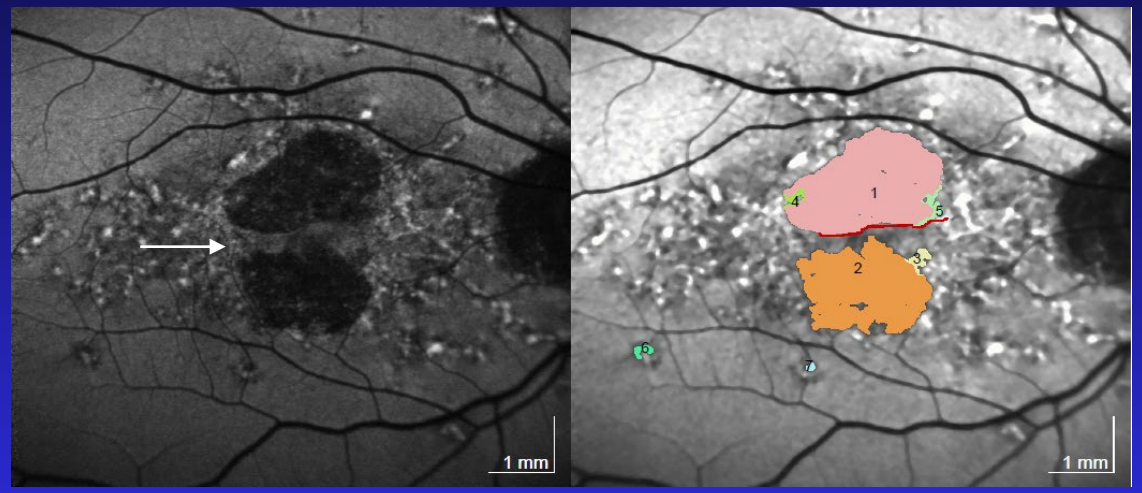
Date:	6/22/2019	Number of regions:	5
Time:	08:25:52	Perilesional pattern:	unseeded
Total region size:	16.484 mm²		

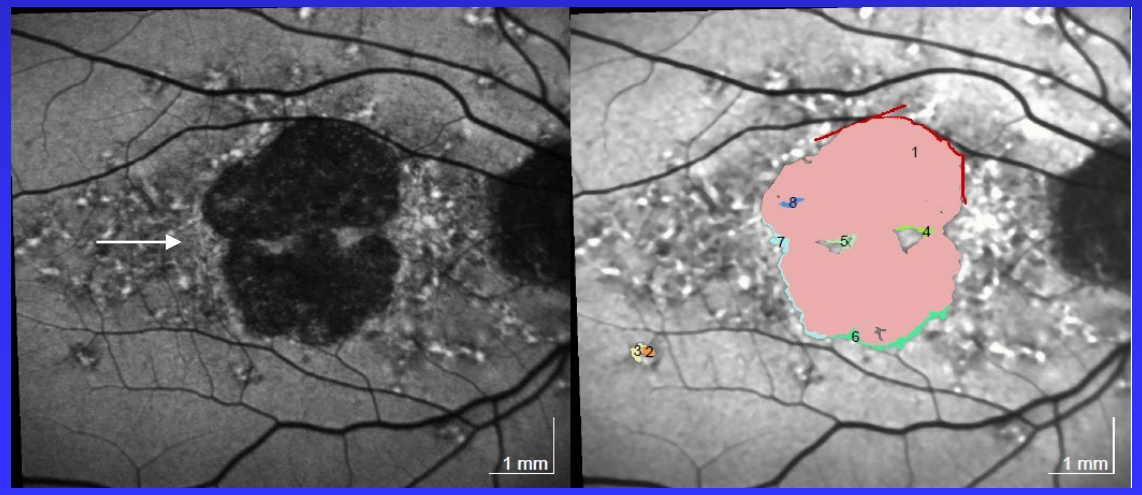
N°	Region Color	Size [mm²]	Growth Power [%]	Growth Limit [%]	Min-Max Vessel [µm]	Strap Ratio
4		8.770	100	100	30 - 30	0.00
3		5.989	100	100	30 - 30	0.00
1		0.898	100	100	30 - 30	0.00
5		0.597	100	100	30 - 30	0.00
2		0.229	100	100	30 - 30	0.00

Notes:

Date: 6/22/2019 Signature:

GA Progression Over Time





Summary

- Robust GA grading methodology
- Experienced Readers
- Most current consensus GA
- Gives confidence in results

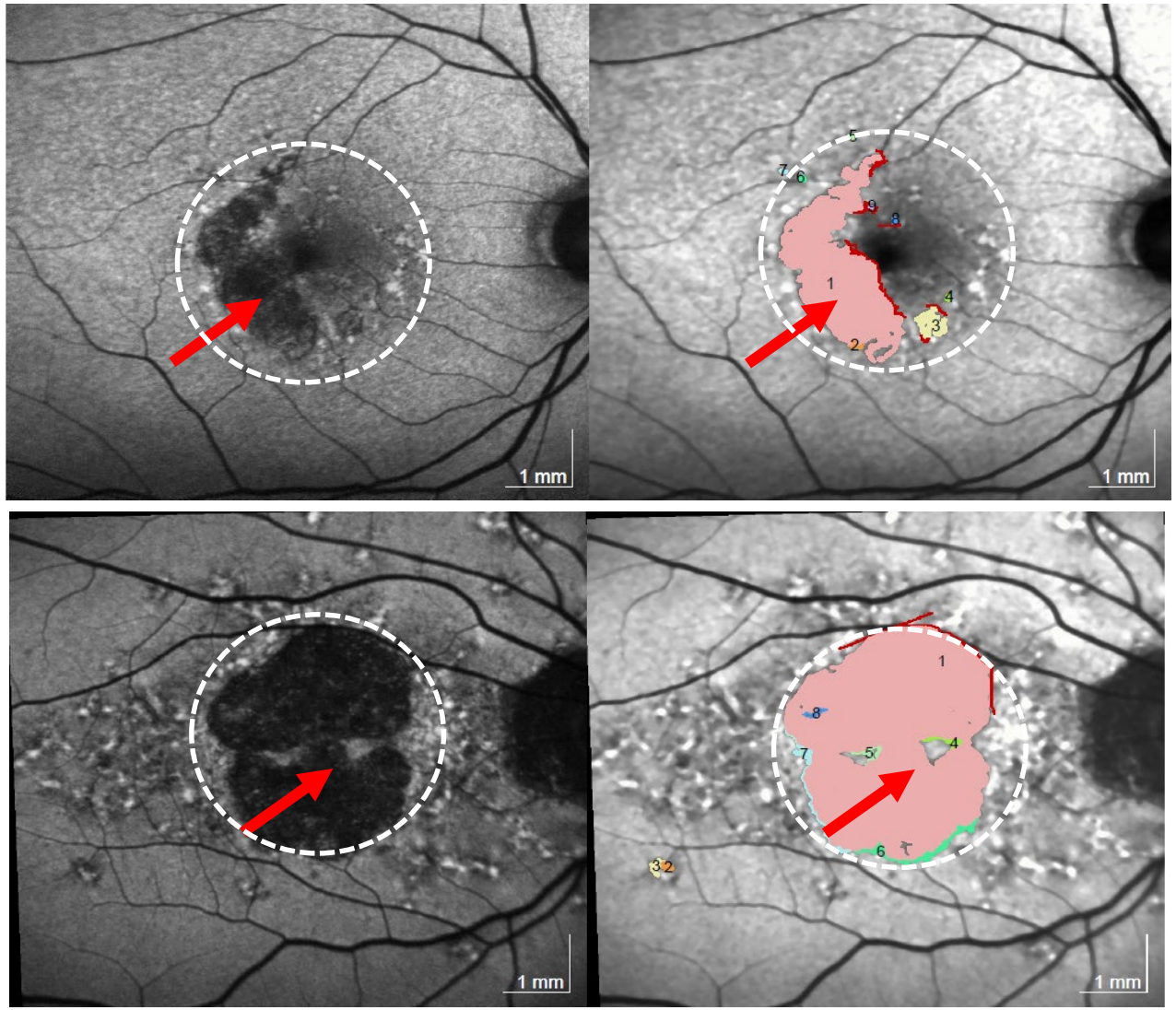
Thank You!

Complement C5 Inhibition: Scientific Rationale in Geographic Atrophy Secondary to Dry AMD

Marco A. Zarbin, M.D., Ph.D., FACS
Professor and Chair
Institute of Ophthalmology and Visual Science
Rutgers-New Jersey Medical School
Newark, New Jersey

Geographic Atrophy:

Degeneration & death of retinal cells over time leading to loss of functional vision



Zimura for Geographic Atrophy: Scientific Rationale

- Complement abnormalities strongly associated with developing AMD:
  - Genetic link
  - In vitro studies
  - Post-mortem ocular histology

- Complement activation → C5 cleavage → C5a & C5b formation
  - **C5a** → **inflammasome activation** → Retinal cell degeneration & cell death
  - **C5b** → **membrane attack complex (MAC) formation** → Retinal cell death

C5 Inhibition: Potential Target for GA and AMD

Genetic Link: Complement & AMD

"In individuals homozygous for the risk allele, the likelihood of AMD is increased by a factor of 7.4"

A common haplotype in the complement regulatory gene factor H (*HF1/CFH*) predisposes individuals to age-related macular degeneration

Gregory S. Hageman[a,b,c], Don H. Anderson[b,d], Lincoln V. Johnson[b,d], Lisa S. Hancox[a], Andrew J. Taiber[a], Lisa I. Hardisty[a], Jill L. Hageman[a], Heather A. Stockman[a], James D. Borchardt[a], Karen M. Gehrs[a], Richard J. H. Smith[e], Giuliana Silvestri[f], Stephen R. Russell[a], Caroline C. W. Klaver[g], Irene Barbazetto[h], Stanley Chang[h], Lawrence A. Yannuzzi[h], Gaetano R. Barile[h], John C. Merriam[h], R. Theodore Smith[h], Adam K. Olsh[i], Julie Bergeron[i], Jana Zernant[h], Joanna E. Merriam[h], Bert Gold[i], Michael Dean[i], and Rando Allikmets[h,k,l]

Source: Proc Natl Acad Sci U S A 2005, 102(20), 7227-7232

Complement Factor H Polymorphism and Age-Related Macular Degeneration

Albert O. Edwards,[1*†] Robert Ritter III,[1] Kenneth J. Abel,[2] Alisa Manning,[3] Carolien Panhuysen,[3,6] Lindsay A. Farrer[3,4,5,6,7]

Source: Science 2005, 308(5720), 421-424

Complement Factor H Polymorphism in Age-Related Macular Degeneration

Robert J. Klein,[1] Caroline Zeiss,[2*] Emily Y. Chew,[3*] Jen-Yue Tsai,[4*] Richard S. Sackler,[1] Chad Haynes,[1] Alice K. Henning,[5] John Paul SanGiovanni,[3] Shrikant M. Mane,[6] Susan T. Mayne,[7] Michael B. Bracken,[7] Frederick L. Ferris,[3] Jurg Ott,[1] Colin Barnstable,[2] Josephine Hoh[7†]

Source: Science. 2005 Apr 15;308(5720):385-389

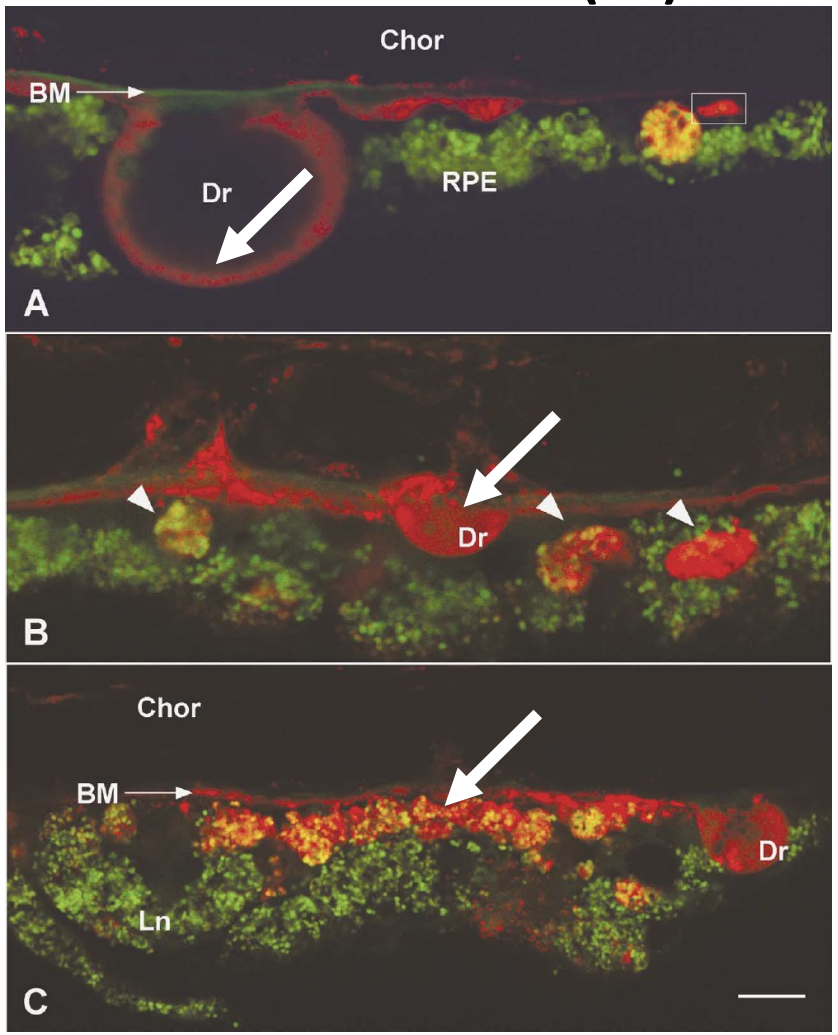
Complement Factor H Variant Increases the Risk of Age-Related Macular Degeneration

Jonathan L. Haines,[1] Michael A. Hauser,[2] Silke Schmidt,[2] William K. Scott,[2] Lana M. Olson,[1] Paul Gallins,[2] Kylee L. Spencer,[1] Shu Ying Kwan,[2] Maher Noureddine,[2] John R. Gilbert,[2] Nathalie Schnetz-Boutaud,[1] Anita Agarwal,[3] Eric A. Postel,[4] Margaret A. Pericak-Vance[2*]

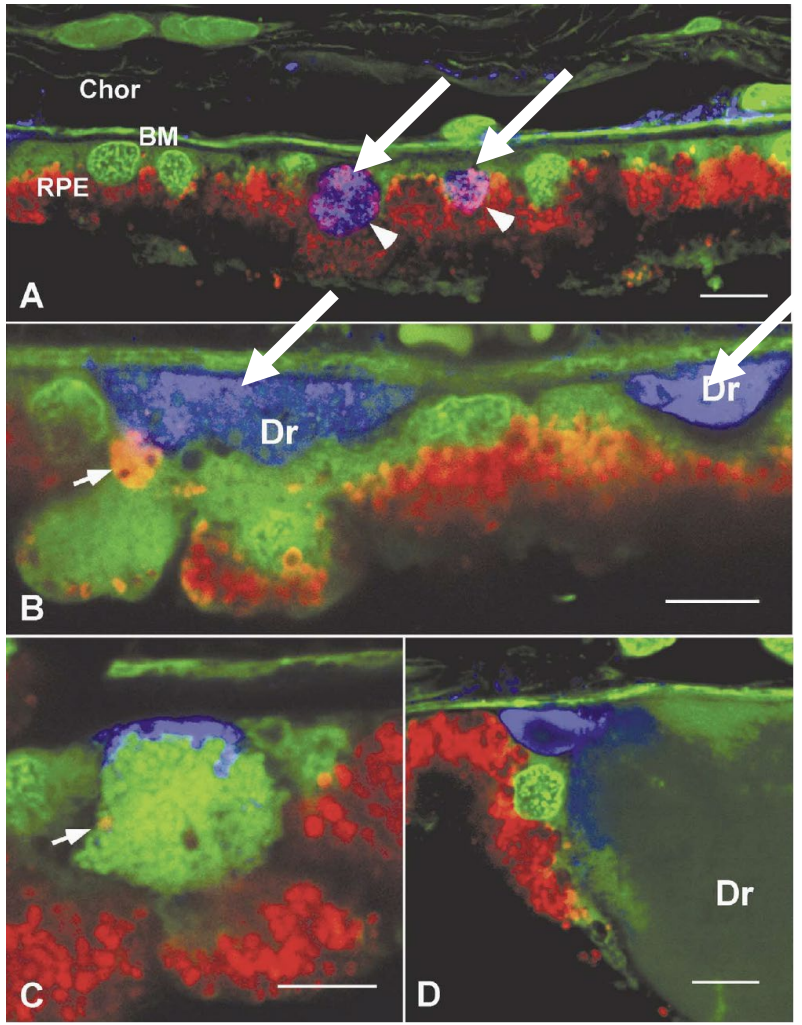
Source: Science 2005, 308(5720), 419-421

Complement in Human AMD Eyes[1]

C5 staining (RED) of RPE & drusen (Dr)



Membrane Attack Complex, C5b-9, MAC (BLUE)

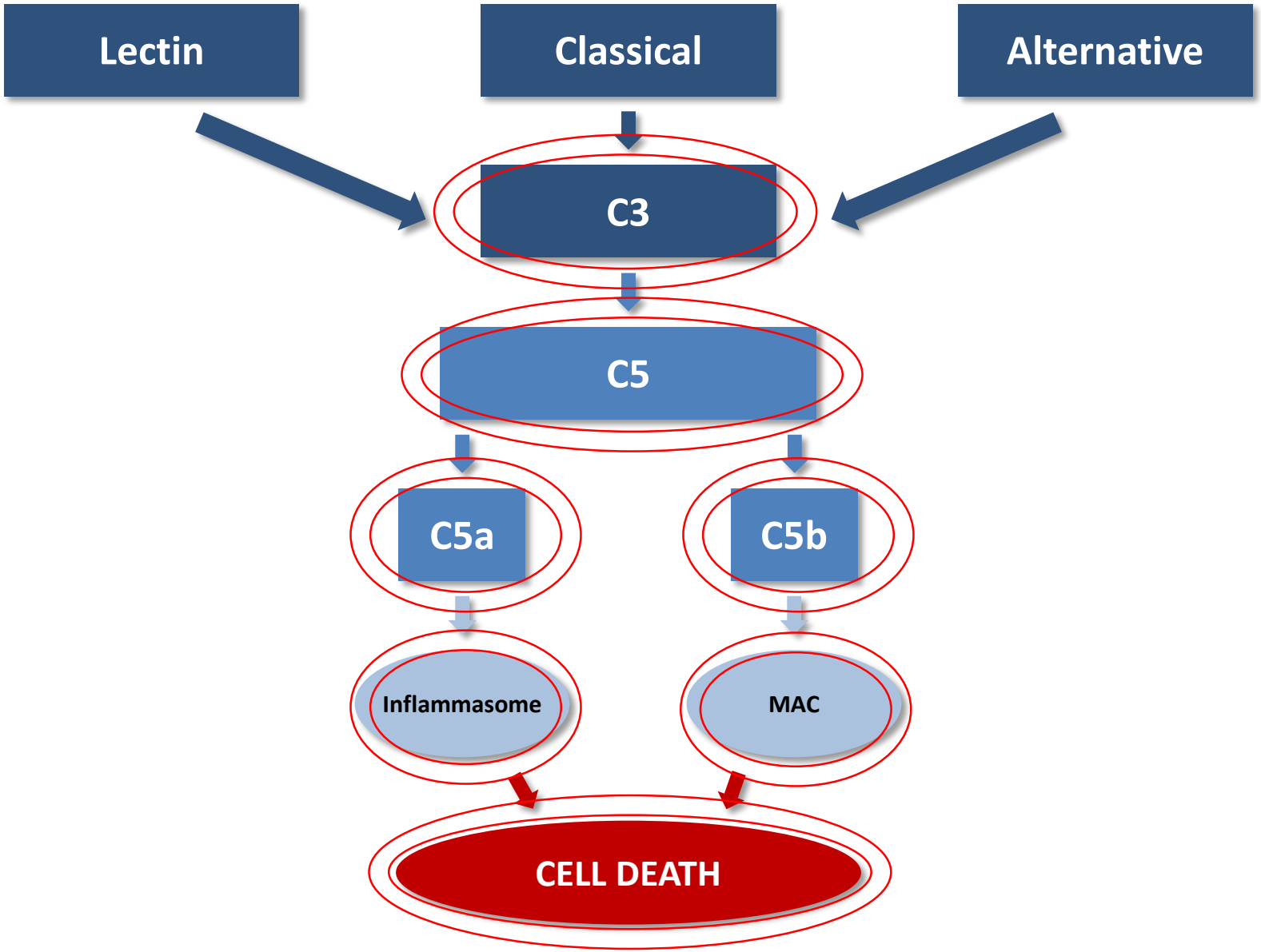


RPE (arrows)

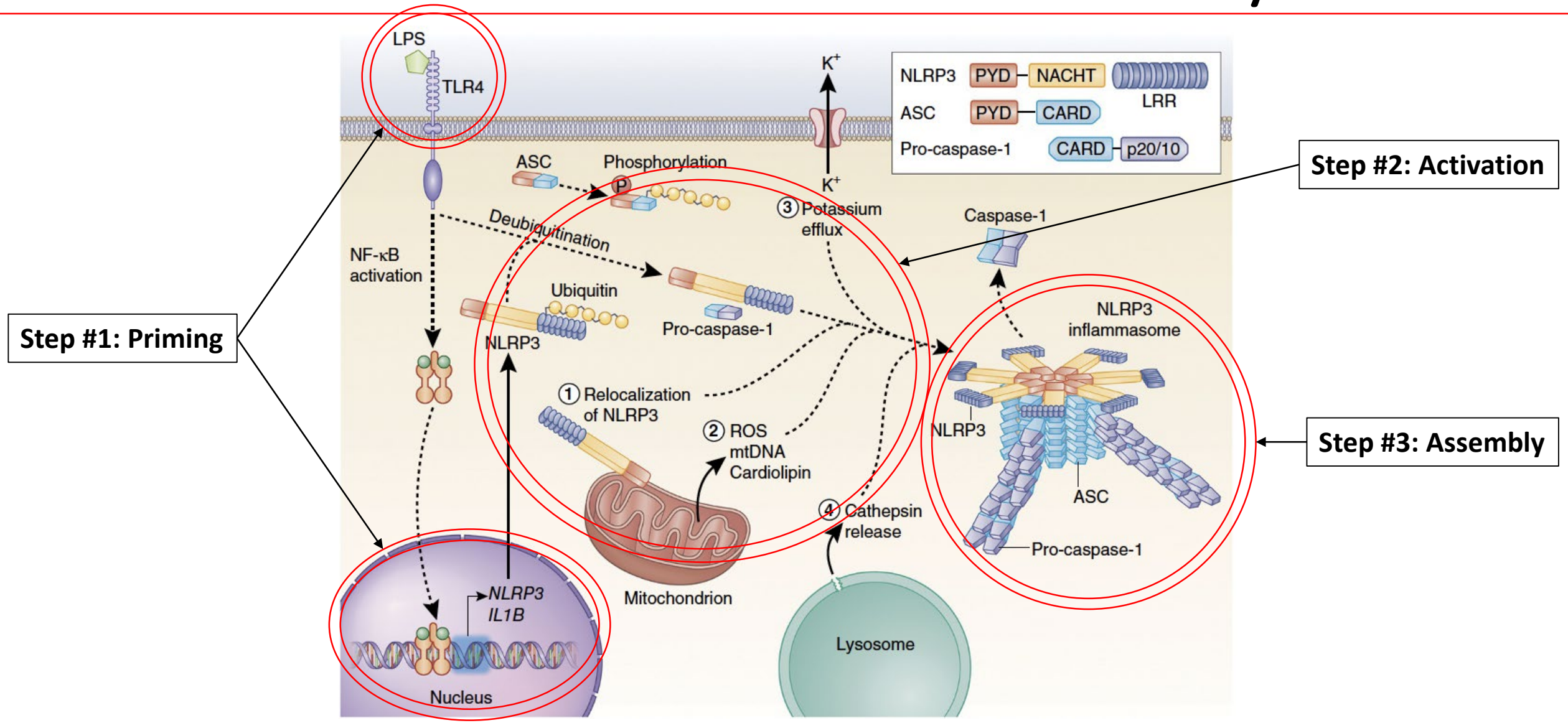
Drusen (Dr)

[1]Anderson DH, Mullins RF, Hageman GS, Johnson LV. A role for local inflammation in the formation of drusen in the aging eye. Am J Ophthalmol 2002;134:411-31.

Complement Pathway: Inflammasome & MAC → Cell Death



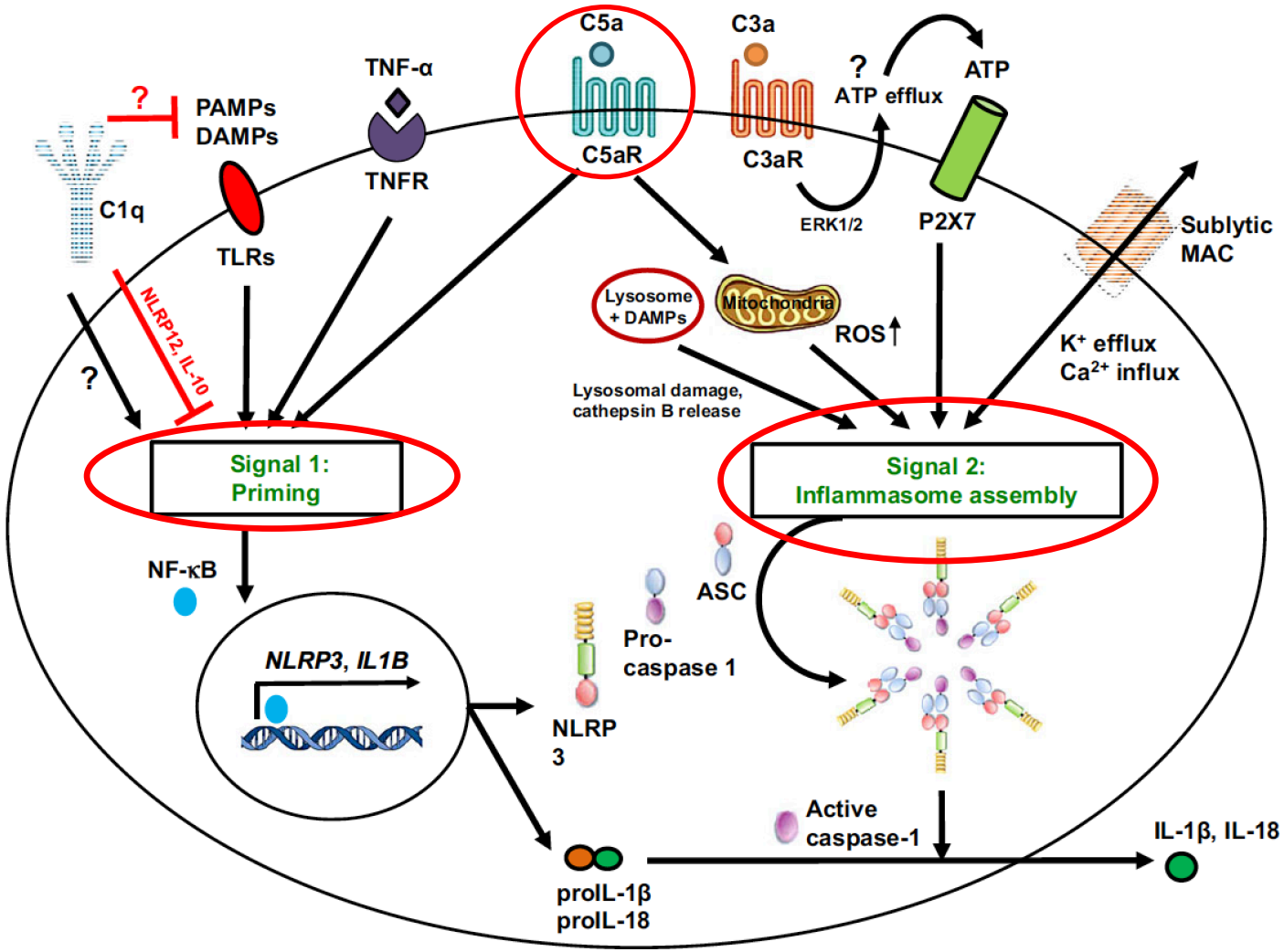
Inflammasome Activation Pathway[1]



NLRP3 inflammasome assembly. CARD, caspase recruitment domain; LRR, leucine-rich repeat; NACHT/NBD, nucleotidd binding domain; PYD, pyrin domain; CAP1, caspase-1, NF-kB, nuclear factor kappa B.

[1]Guo H, Callaway JB, Ting JP. Inflammasomes: mechanism of action, role in disease, and therapeutics. Nat Med 2015;21(7):677-87

C5a Contributes to Inflammasome Priming & Activation[1]



[1]Arbore G, Kemper C. A novel "complement-metabolism-inflammasome axis" as a key regulator of immune cell effector function. Eur J Immunol 2016;46(7):1563-73.

C5a: Inflammasome & RPE Cells

- C5a: a priming agent for inflammasome activation in RPE cells
  - C5a upregulates inflammasome-related genes

- Inflammasome activation: → ↑ levels IL-1β & IL-18 (**both induce RPE degeneration**)

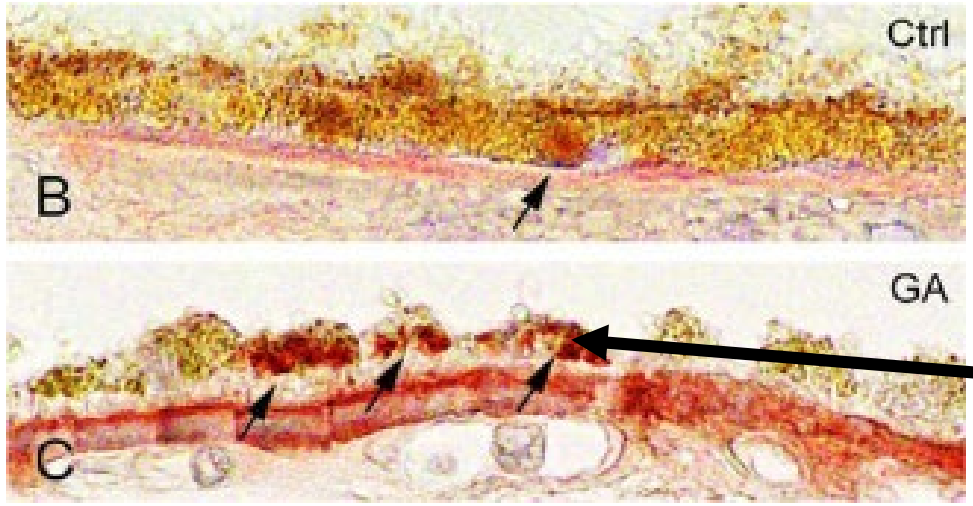
- NLRP3 Inflammasome, IL-1β & IL-18 are present in post mortem eyes with geographic atrophy secondary to dry AMD

Sources:
Br J Ophthalmol. 2016 May ; 100(5): 713–71; Invest Ophthalmol Vis Sci. 2013;54:110–120.; Br J Ophthalmol. 2016 May ; 100(5): 713–718; Investigative Ophthalmol Vis Sci. 2014, 55, 6673-6678.; The Journal of Biological Chemistry. 2015;290: 52: 31189-31198.

IL-1β & IL-18 Immunoreactivity in RPE Cells in Eyes with GA[1]

Control

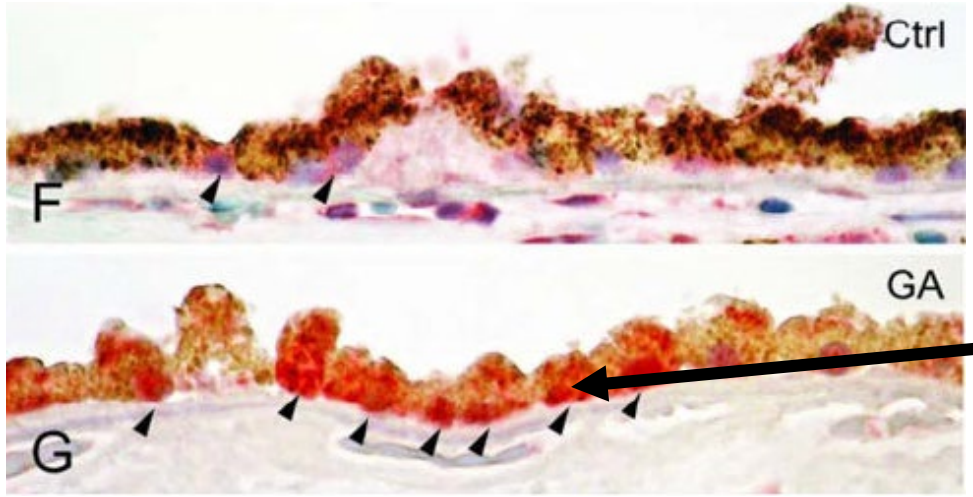
Geographic Atrophy



IL-1β

Control

Geographic Atrophy

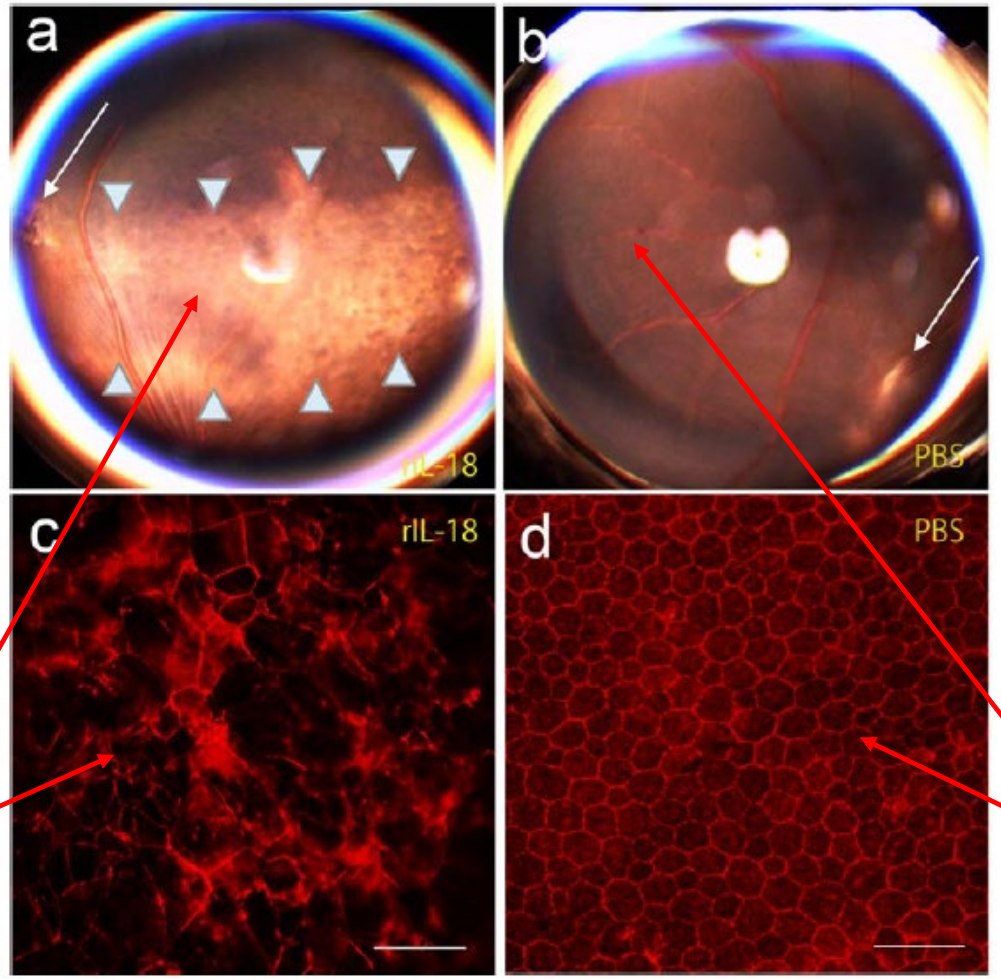


IL-18

[1]Cao S, Wang JC, Gao J, et al. CFH Y402H polymorphism and the complement activation product C5a: effects on NF-kappaB activation and inflammasome gene regulation. Br J Ophthalmol 2016;100(5):713-8

IL-18 Induces RPE Degeneration in Wild Type Mouse[1]

7 days after subretinal injection of 1 μg mouse recombinant IL-18

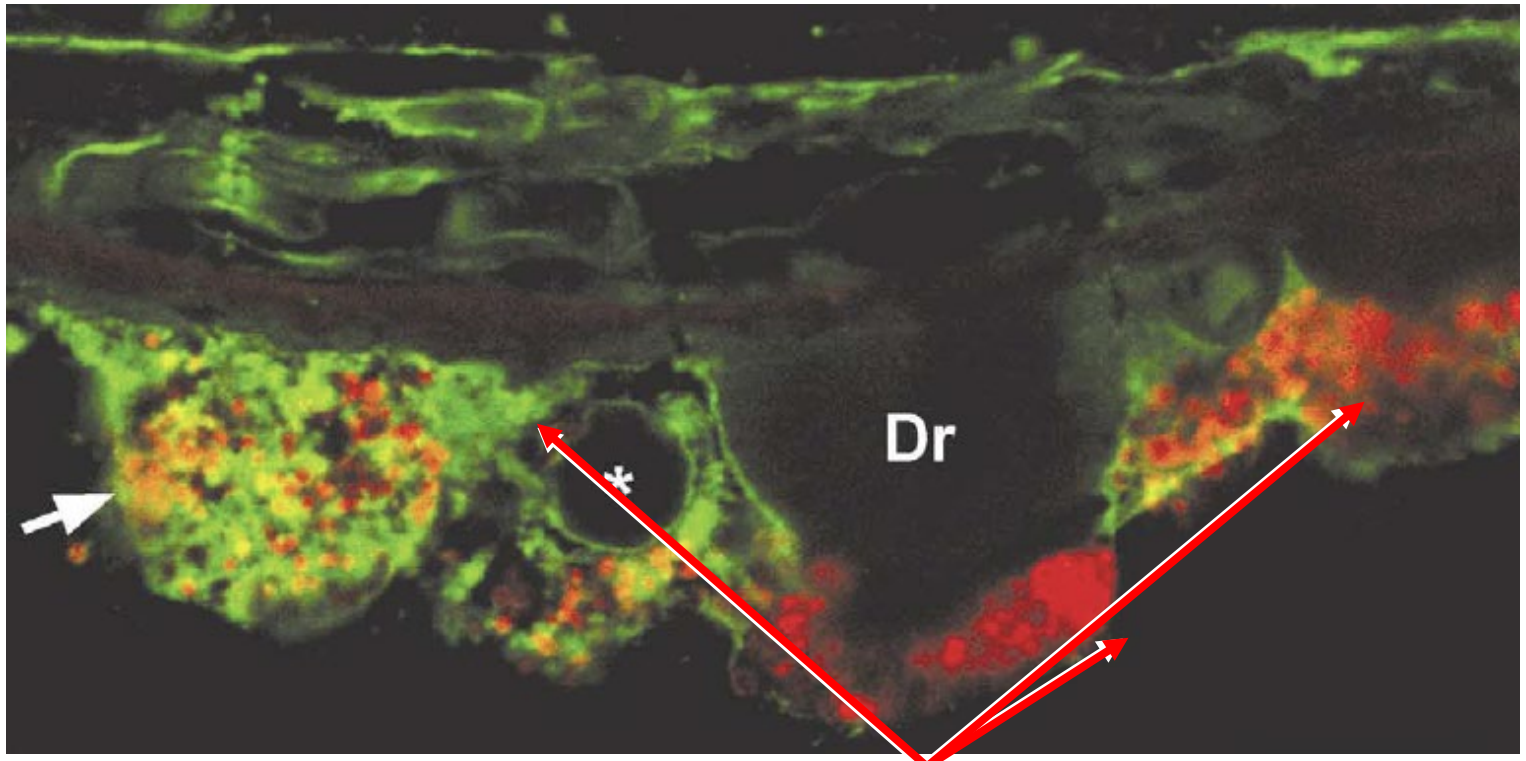


Strongly Damaged Retinal Pigment Epithelium

Healthy Retinal Pigment Epithelium

[1]Ijima R, Kaneko H, Ye F, et al. Interleukin-18 induces retinal pigment epithelium degeneration in mice. Invest Ophthalmol Vis Sci 2014;55(10):6673-8

Lipofuscin Accumulation in RPE[1]



Lipofuscin (age related waste: red particles) in RPE adjacent to & overlying drusen (Dr)

[1]Anderson DH, Mullins RF, Hageman GS, Johnson LV. A role for local inflammation in the formation of drusen in the aging eye. Am J Ophthalmol 2002;134(3):411-31.

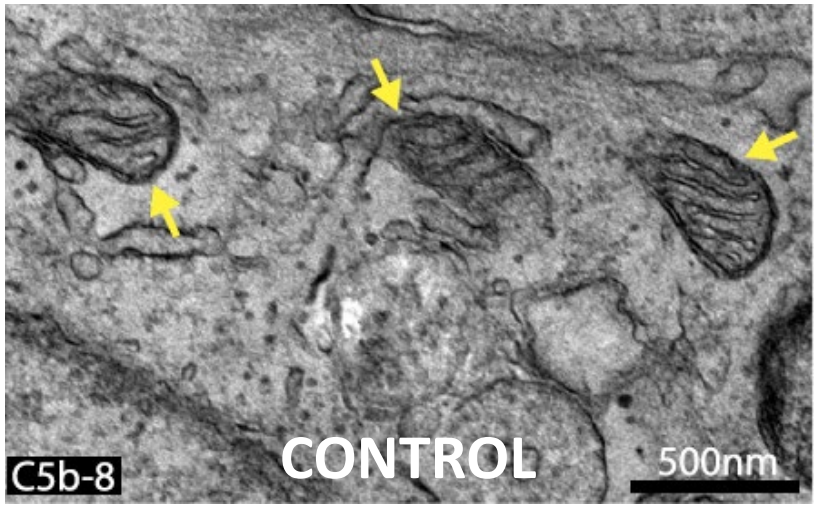
C5b: MAC & RPE Cells

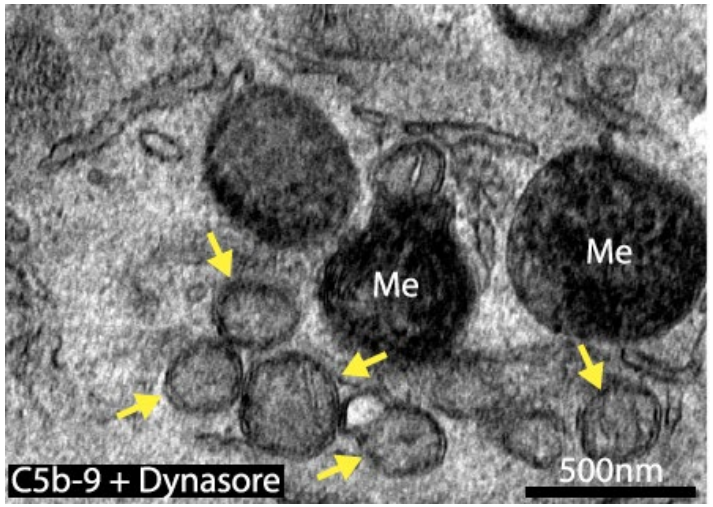
- A2E, a component of lipofuscin (age-related waste product), activates complement.[1]
- A2E accumulation leads to lysosomal dysfunction & mitochondrial damage.[2,3]
- MAC is cleared by endocytic pathway & lysosomal degradation.[4]
- A2E accumulation prevents the clearance of MAC in RPE cells.[5]
- MAC is present in drusen & RPE of post mortem eyes in patients with dry AMD

[1]Zhou J, Jang YP, Kim SR, et al. Complement activation by photooxidation products of A2E, a lipofuscin constituent of the retinal pigment epithelium. Proc Natl Acad Sci U S A 2006;103:16182-7
[2]Schutt F, Bergmann M, Holz FG, et al. Isolation of intact lysosomes from human RPE cells and effects of A2-E on the integrity of the lysosomal and other cellular membranes. Graefes Arch Clin Exp Ophthalmol 2002;240:983-8.
[3]Bergmann M, Schutt F, Holz FG, et al. Inhibition of the ATP-driven proton pump in RPE lysosomes by the major lipofuscin fluorophore A2-E may contribute to the pathogenesis of age-related macular degeneration. FASEB J 2004;18:562-4.
[4]J Georgiannakis A, Burgoyne T, Lueck K, et al. Retinal Pigment Epithelial Cells Mitigate the Effects of Complement Attack by Endocytosis of C5b-9. J Immunol 2015;195:3382-9
[5]Li W, Chen S, Ma M, Qian J, Ma X. Complement 5b-9 complex-induced alterations in human RPE cell physiology. Med Sci Monit 2010;16:BR17-23

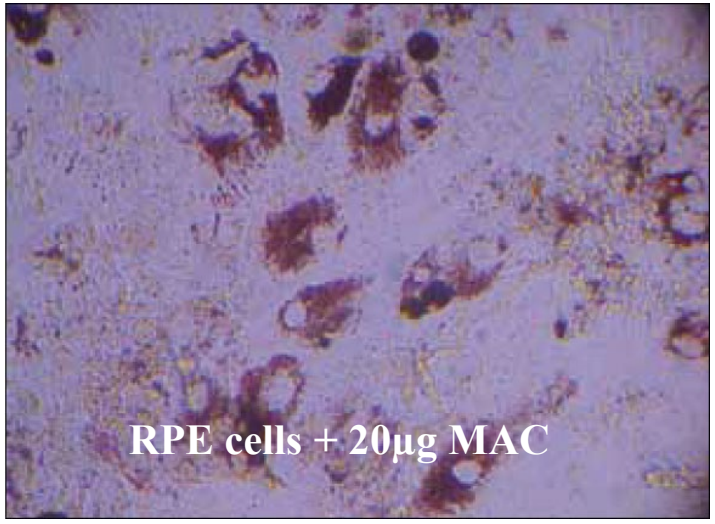
MAC Accumulation: Mitochondrial Damage & RPE Cell Death

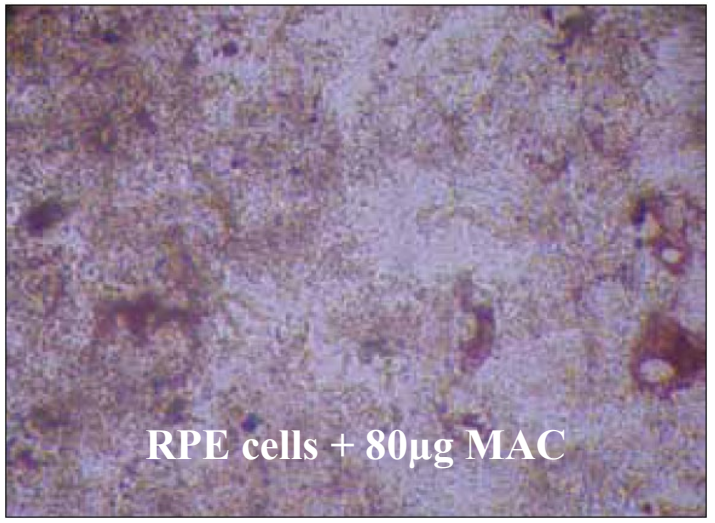
MAC induced mitochondria damage: Fewer & smaller/rounder than typical





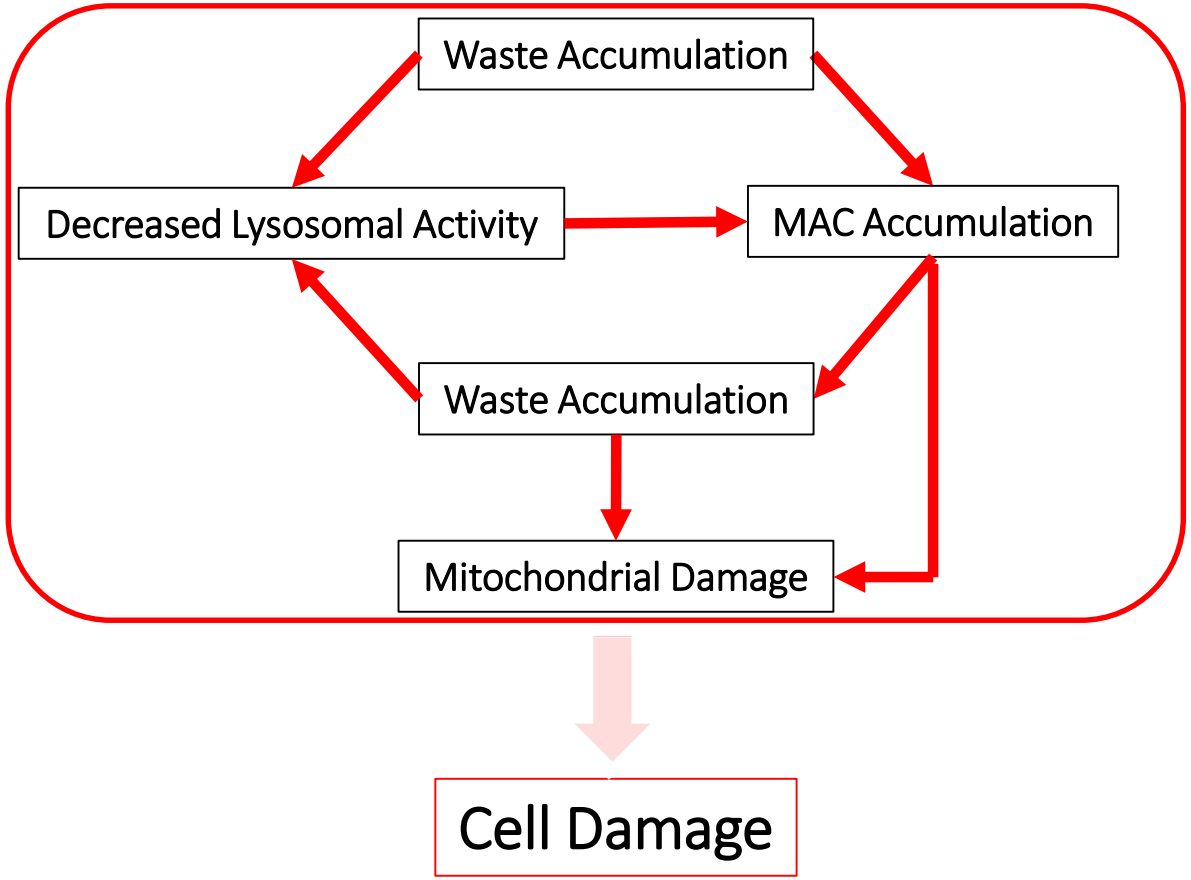
Increased MAC Concentration leads to RPE cell lysis (cell death)





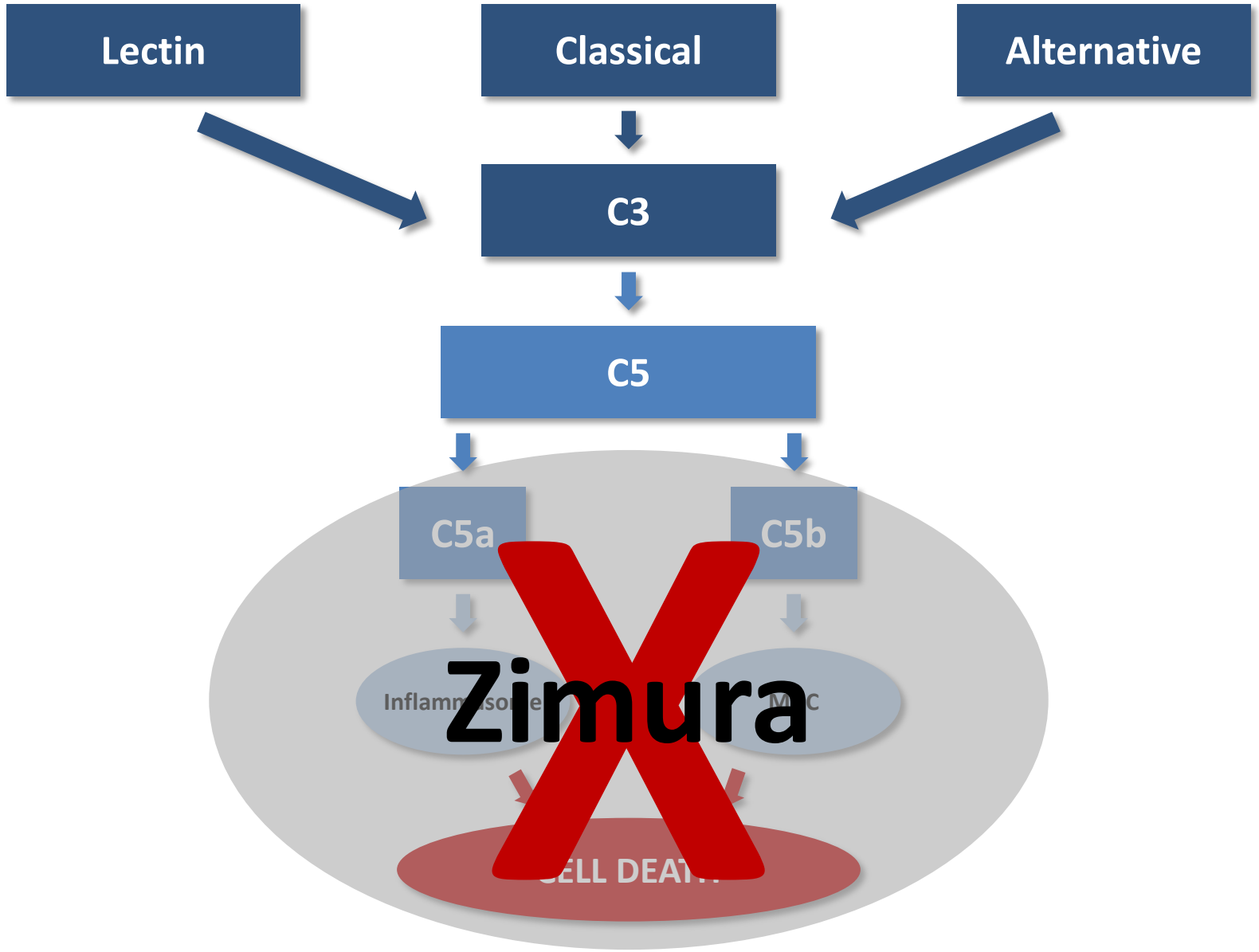
Sources: J Immunol. 2015; 195:3382-3389. Med Sci Monit, 2010; 16(1): BR17-23.

A2E Accumulation → MAC Accumulation



Sources: FASEB J. 2004; 18(3):562-4. Graefe's Arch Clin Exp Ophthalmol. 2002; 240:983–988. Proc Natl Acad Sci U S A. 2006; 103(44):16182-7. Invest Ophthalmol Vis Sci. 2009; 50(3): 1392–1399. J Immunol 2015; 195:3382-3389. The Journal of Biological Chemistry. 2011; 286(21): 18593–18601. Proc Natl Acad Sci U S A. 2017; 114(15):3987-3992. Invest Ophthalmol Vis Sci. 2013; 54:2669–2677. ARVO 2016: #6592 – D0363.

Complement Activation→ ↑Inflammasome & MAC X Cell Death



The importance of preserving C3-C3a receptor signalling

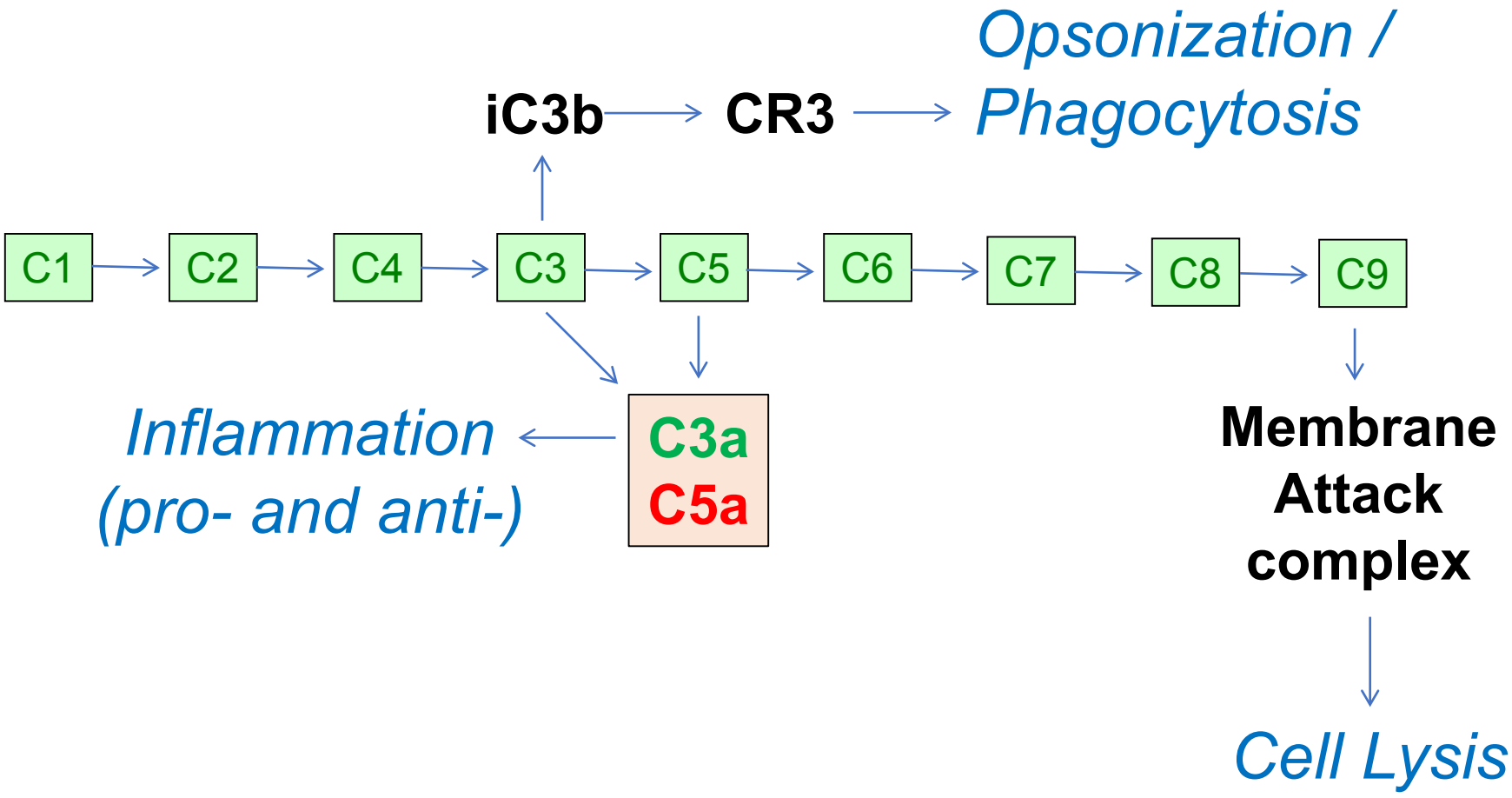
Implications for therapeutic targeting of complement

Trent M. Woodruff, PhD

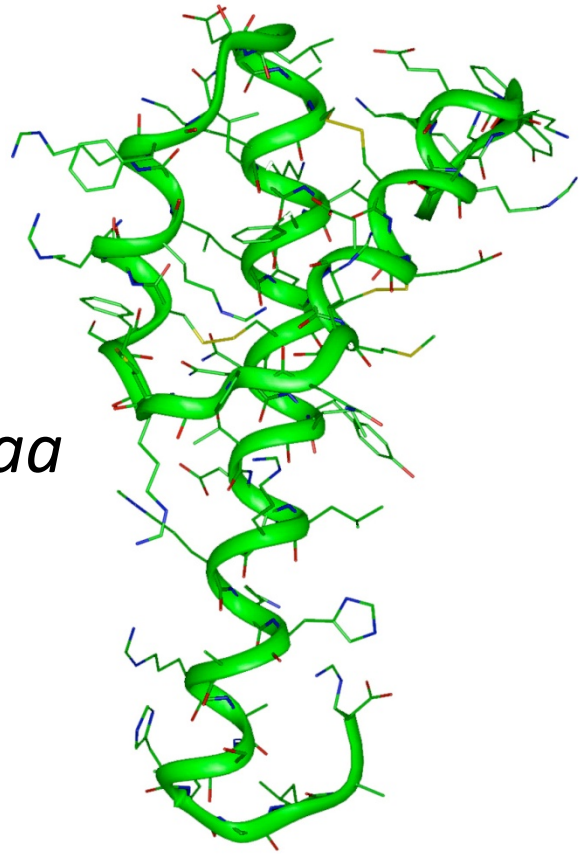
Professor of Pharmacology

The University of Queensland,
Brisbane, Australia

Complement Activation



Background: Anaphylatoxins



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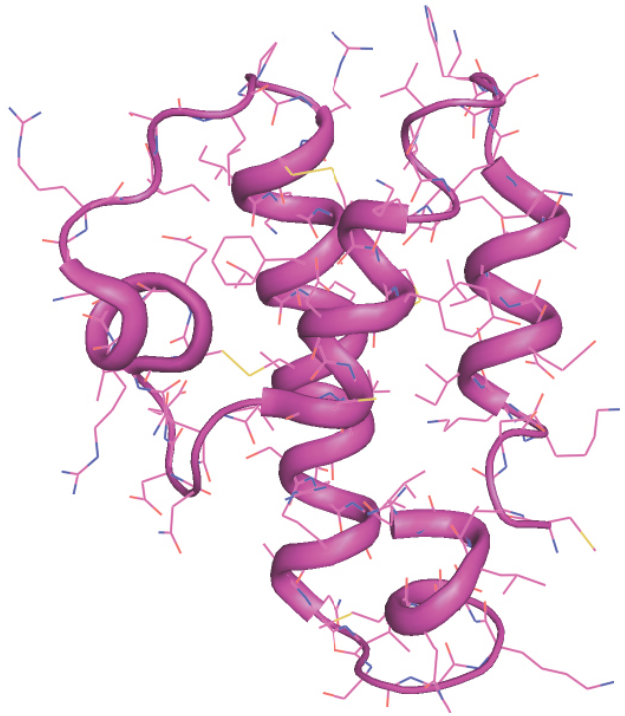
C3a



74aa

C5a

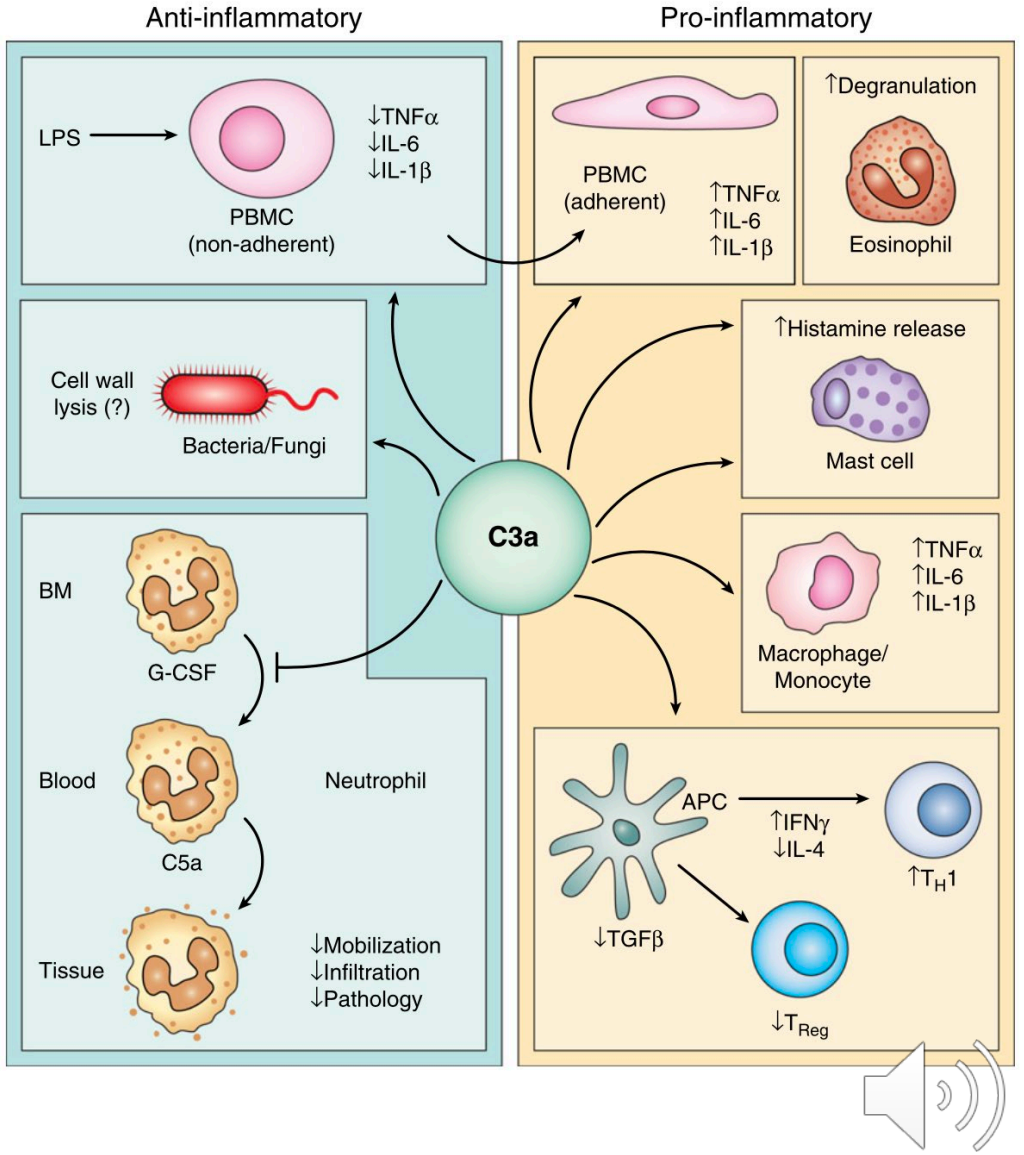
Lambris and Morikis, 2005. Structural Biology of the complement System, CRC Press

Background: C3a and C5a

- Pro-inflammatory mediators
- Chemotaxis → cell activation → release of inflammatory mediators

Cell Type	C3a	C5a
Mast cell	✓	✓
Monocyte	✓ ✗	✓
Neutrophil	✗	✓

- *In vivo?*

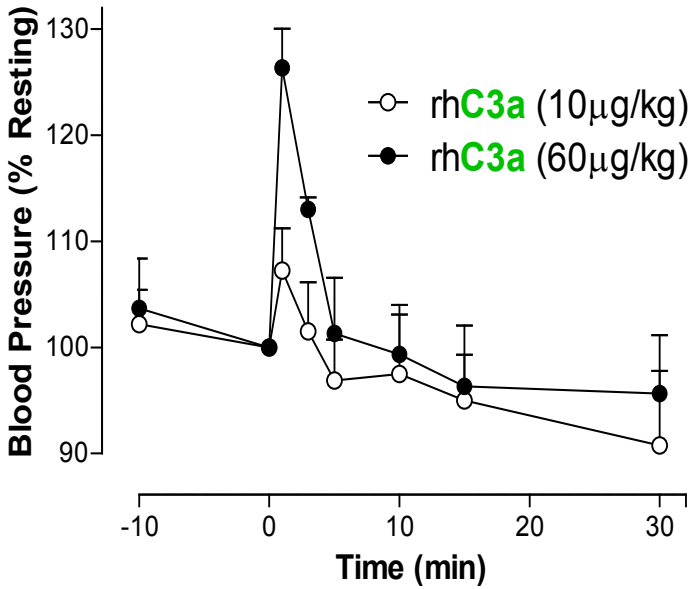


Coulthard, Woodruff (20015) *J Immunol*

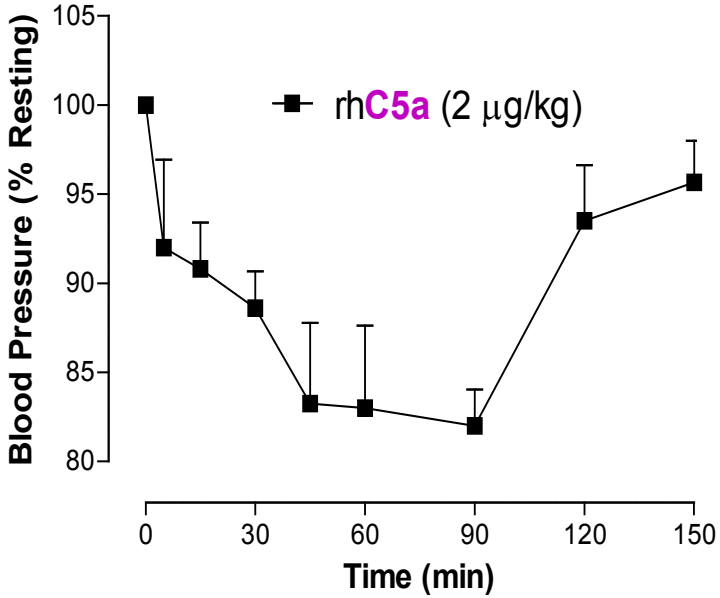
C3a and C5a *in vivo*

- C3a and C5a injected intravenously

Opposing actions on blood pressure



C3a = Hypertension

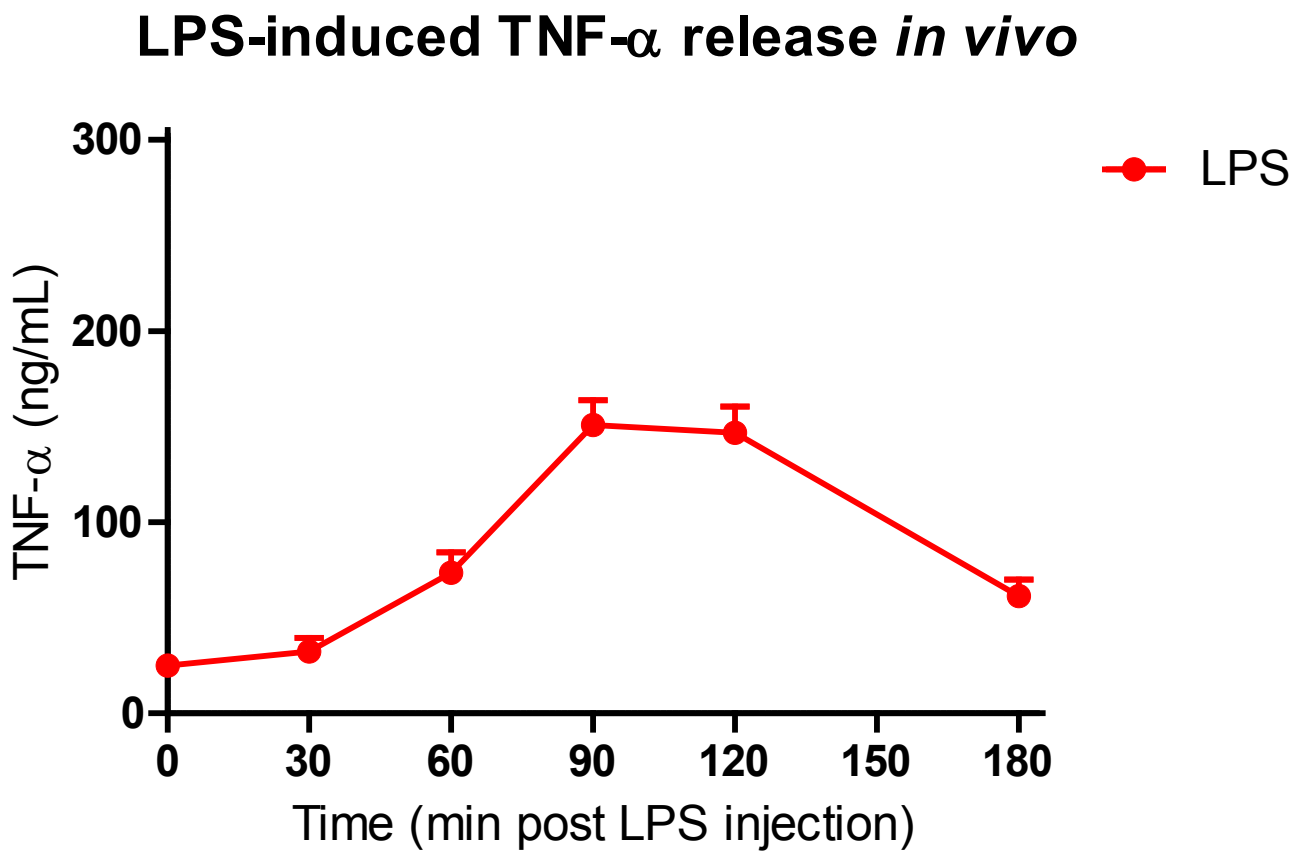


C5a = Hypotension

Proctor et al., Woodruff (2009) *Int Immunopharm*. 9:800-6

C3a and C5a: Opposing Roles

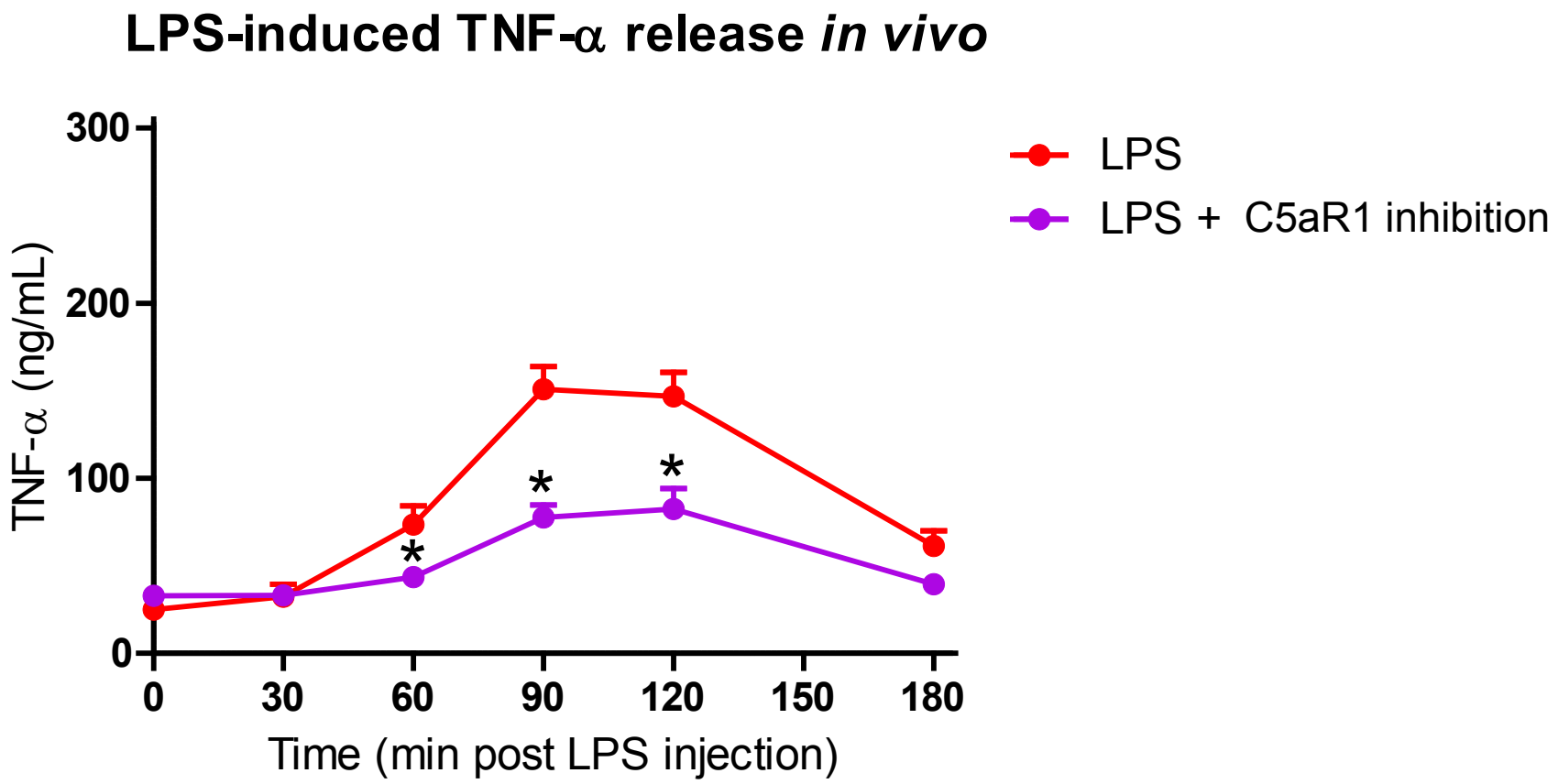
Septic Shock



Woodruff et al., *unpublished*

C3a and C5a: Opposing Roles

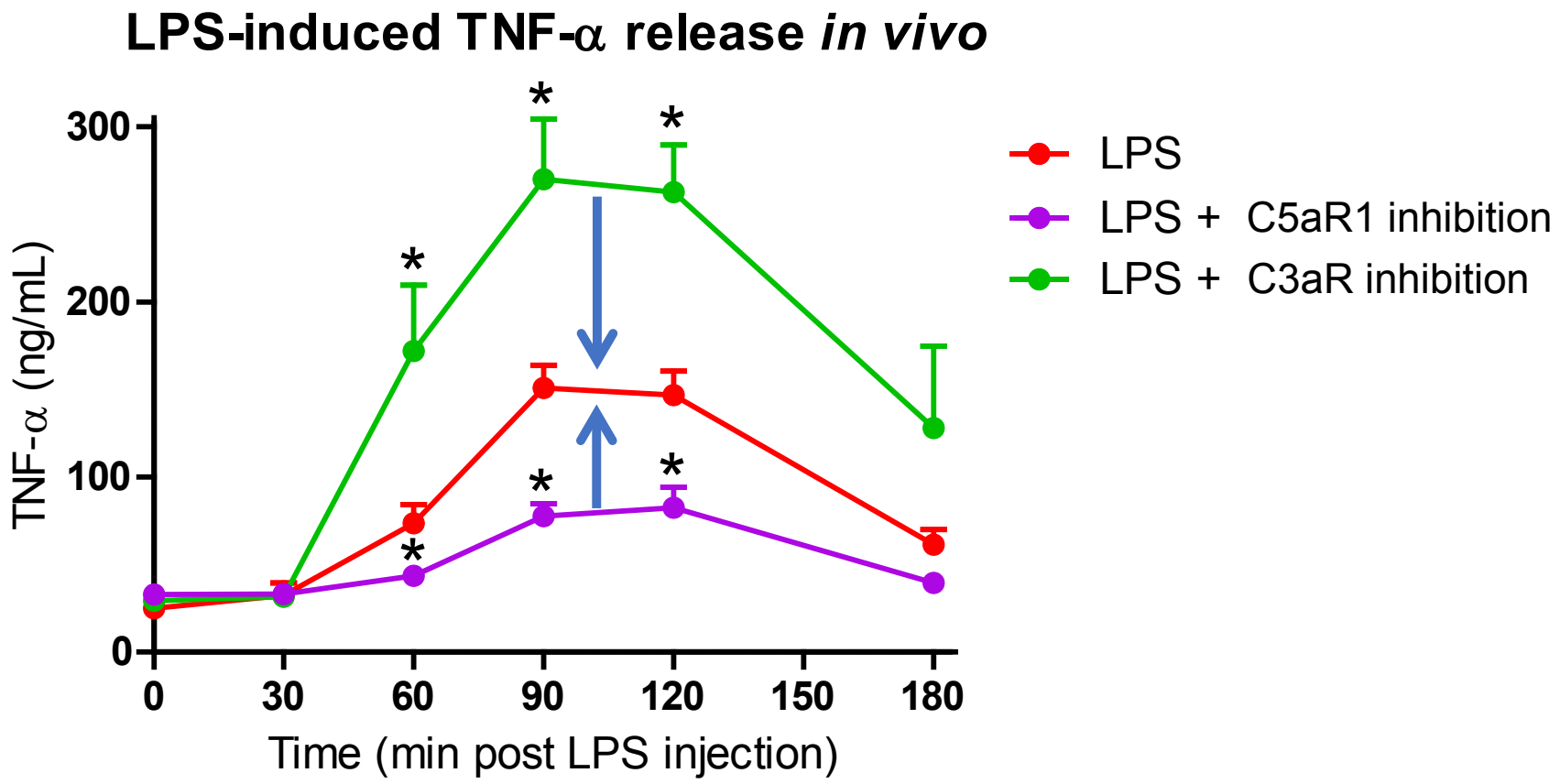
Septic Shock



Woodruff et al., *unpublished*

C3a and C5a: Opposing Roles

Septic Shock



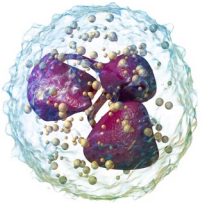
C3a reduces cytokine release → Anti-inflammatory

Physiological Antagonism

C5a enhances cytokine release → Pro-inflammatory

Woodruff et al., *unpublished*

C3aR and neutrophils



Neutrophil

- C3aR abundantly expressed by neutrophils
- C3a not chemotactic for neutrophils!
- C3a doesn't induce 'activation' of neutrophils

- *Question: What is C3aR doing on neutrophils?*

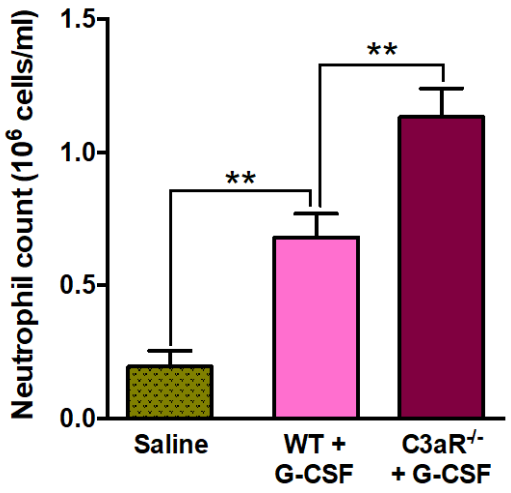
- *Answer: C3aR activation inhibits neutrophil mobilization from the bone marrow*

C3aR is protective on neutrophils

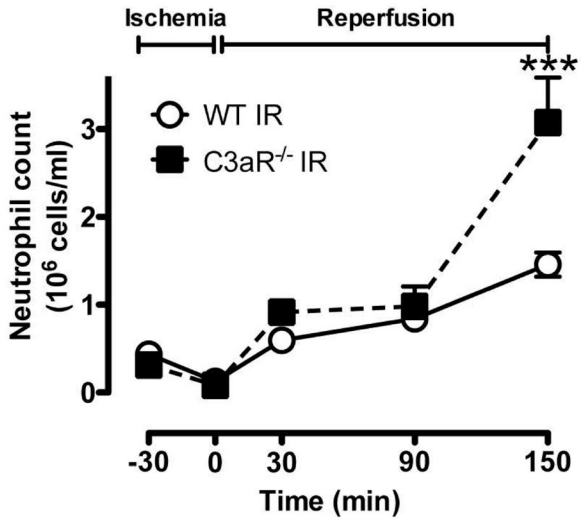
Neutrophils

- **C3aR** – prevents neutrophil mobilization and subsequent infiltration into tissues

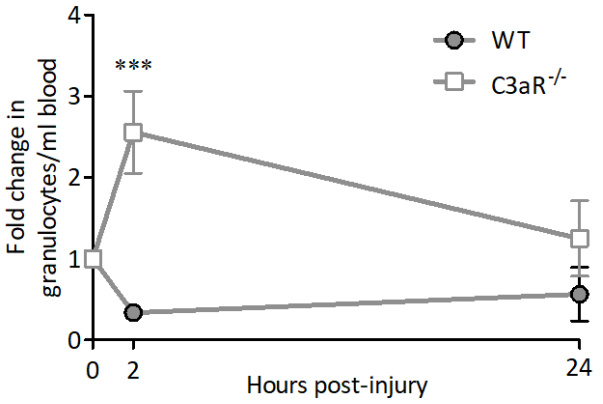
G-CSF



Intestinal I/R

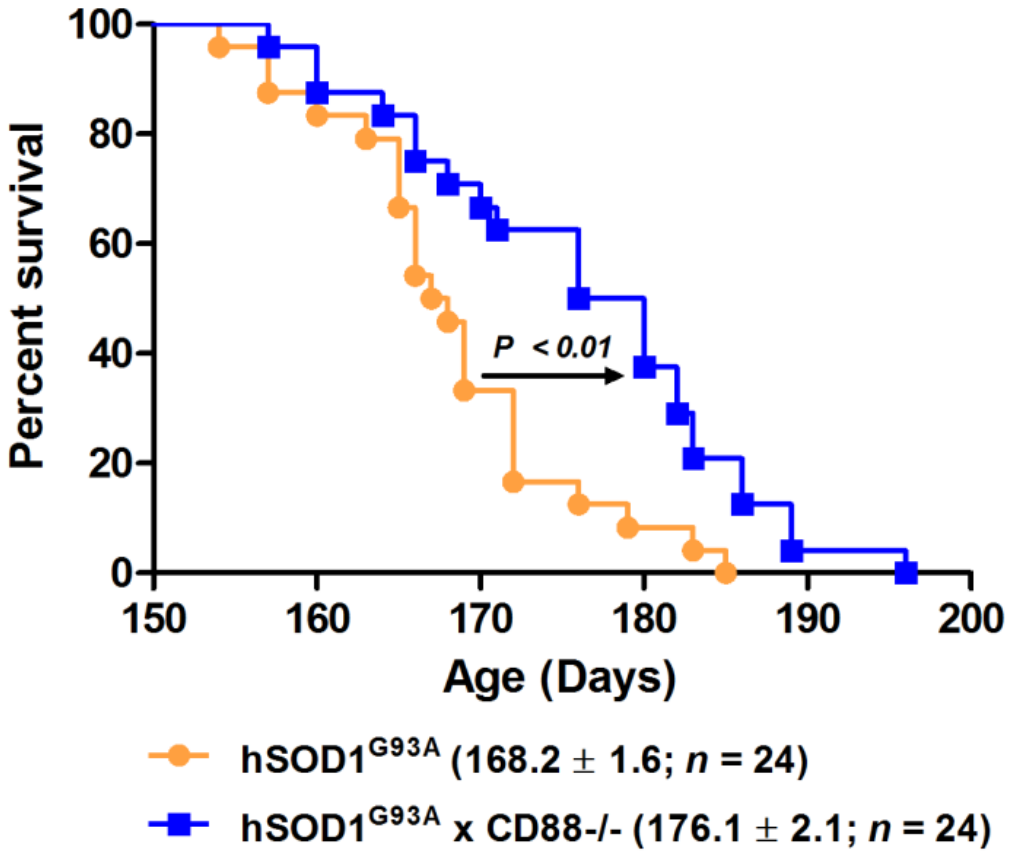


Spinal cord injury



Wu et al., 2013, *PNAS*; Brennan et al., 2019, *JCI Insight*

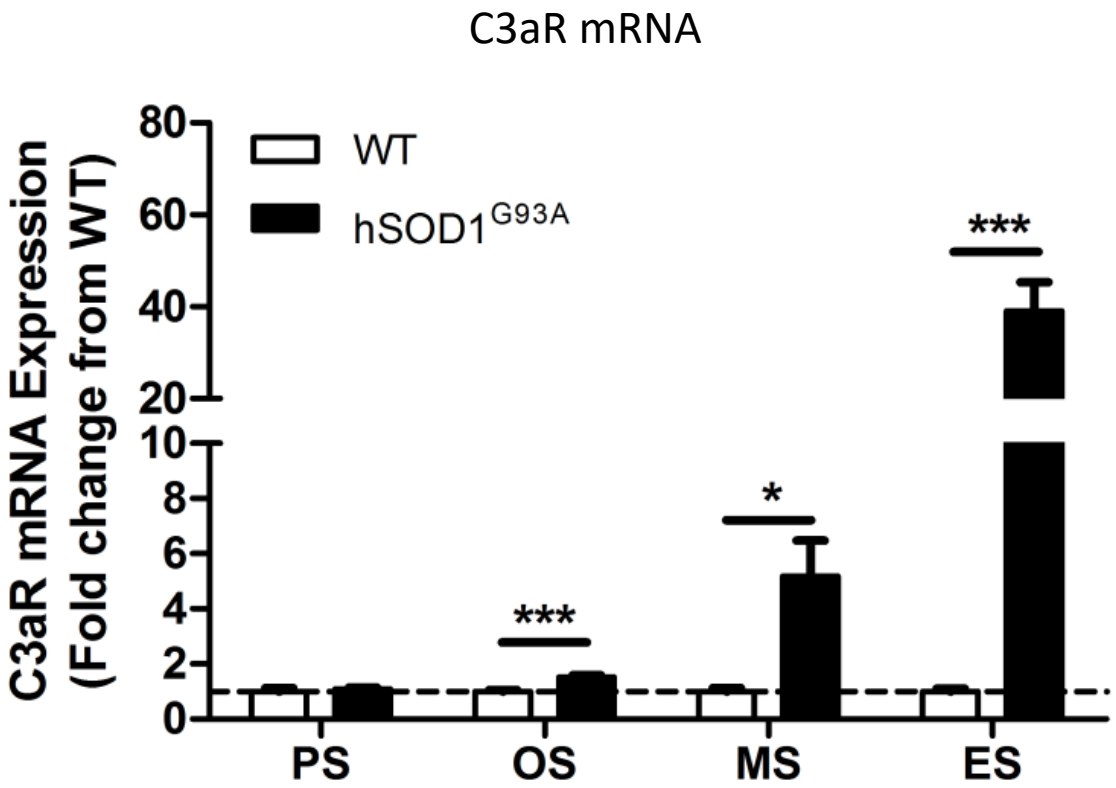
C5a in ALS: C5aR1$^{-/-}$ SOD1^{G93A} mice



Genetic absence of C5aR increases survival and slows motor neuron death in SOD1^{G93A} mice

Woodruff et al., 2014, *PNAS.*11(1):E3-4

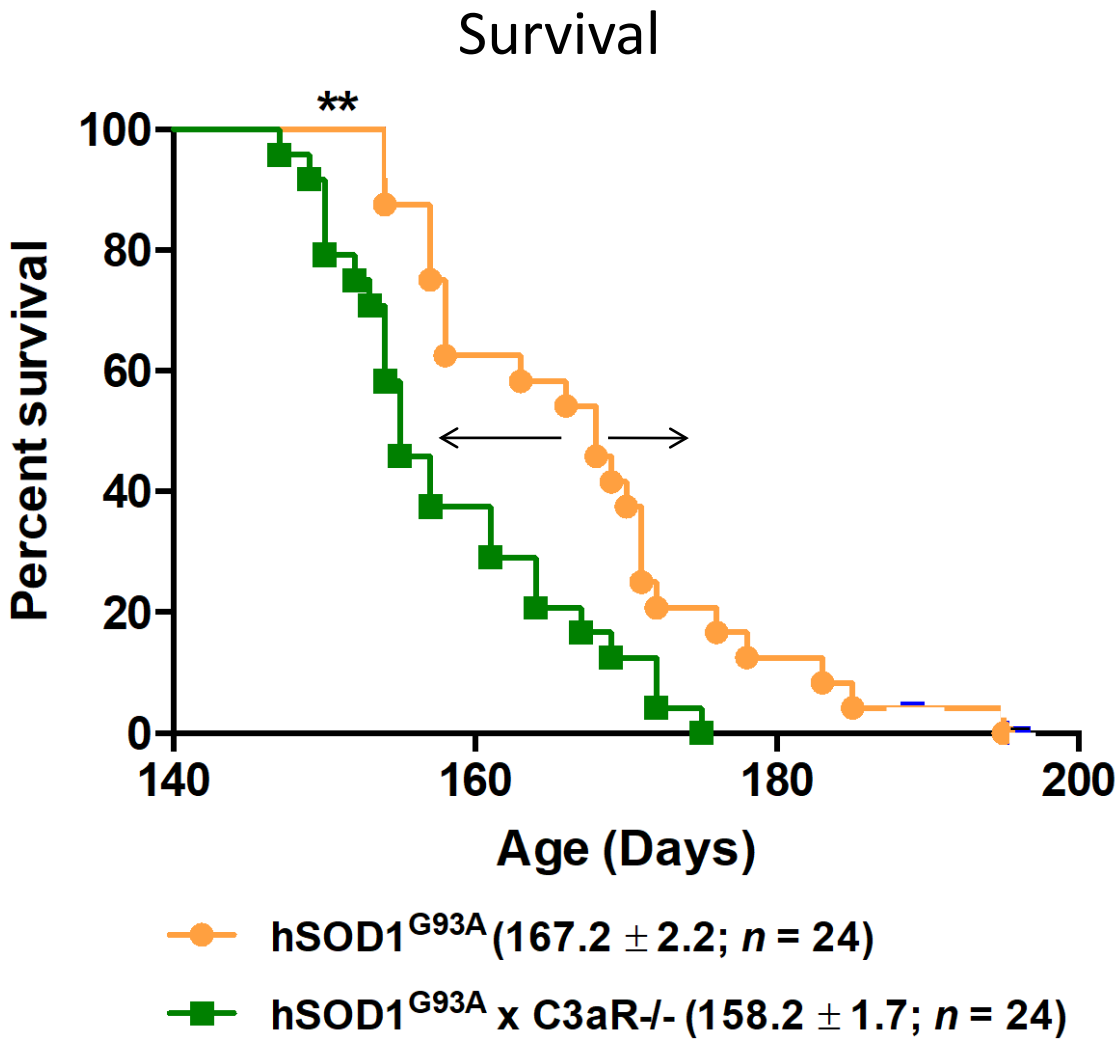
C3a in ALS: A similar or opposing role in ALS?



C3aR are upregulated in diseased SOD1^{G93A} mice

Woodruff et al., *unpublished*

C3a in ALS: C3aR$^{-/-}$ SOD1^{G93A} mice



Genetic absence of C3aR reduces survival in SOD1^{G93A} mice

Woodruff et al., *unpublished*

Protective roles for C3 in the eye: iC3b-CR3

- Absence of C3 accelerated photoreceptor degeneration in the rd10 mouse model of *retinitis pigmentosa*
- Absence of microglial CR3 also recapitulated the phenotype
- Implicates iC3b opsonization of apoptotic photoreceptors and phagocytic clearance by microglia through CR3
- Early clearance of apoptocic photoreceptors, reduces inflammation and non-cell autonomous degeneration

Silverman et al., *J Exp Med*

Protective roles for C3 in infection control

- All complement components contribute to immune defense
- C3 plays roles through both C3a and iC3b
- Several examples where C3 (but not C5) are important for immune protection

Complement Component C3 Is Required for Protective Innate and Adaptive Immunity to Larval *Strongyloides stercoralis* in Mice

Laura A. Kerepesi, Jessica A. Hess, Thomas J. Nolan, Gerhard A. Schad and David Abraham

J Immunol 2006; 176:4315-4322; ;

- Selective targeting of pathogenic complement components may avoid opportunistic infection risk

Summary

- Complement C3a receptors play roles in endotoxemia, ischemia-reperfusion, neurotrauma, and ALS models
- ***C3aR*** *is protective* in these models (knockout worsens disease)
- ***C3-CR3*** *is also protective* in the eye in retinitis pigmentosa model
- Global blockade of C3 (as opposed to C5) may prevent the beneficial activities of C3a, whilst also increasing infection risk
- Complement drugs should therefore targeted towards disease indication to provide appropriate therapeutic response

Potential For Complement Inhibition Beyond Geographic Atrophy

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University of Southern California
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Managing Partner
Retinal Consultants of Arizona
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Founding Partner
Spectra Eye Institute
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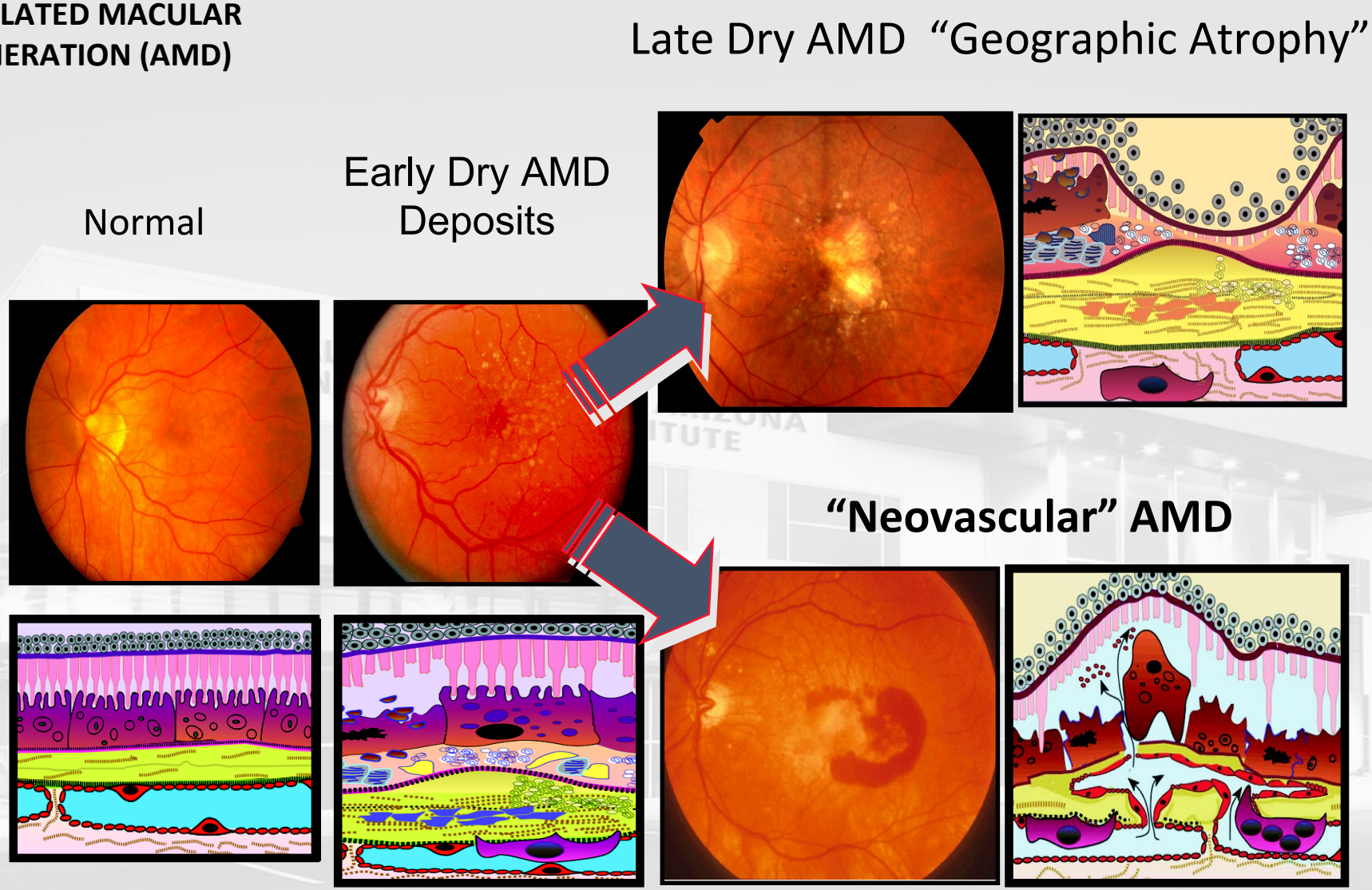
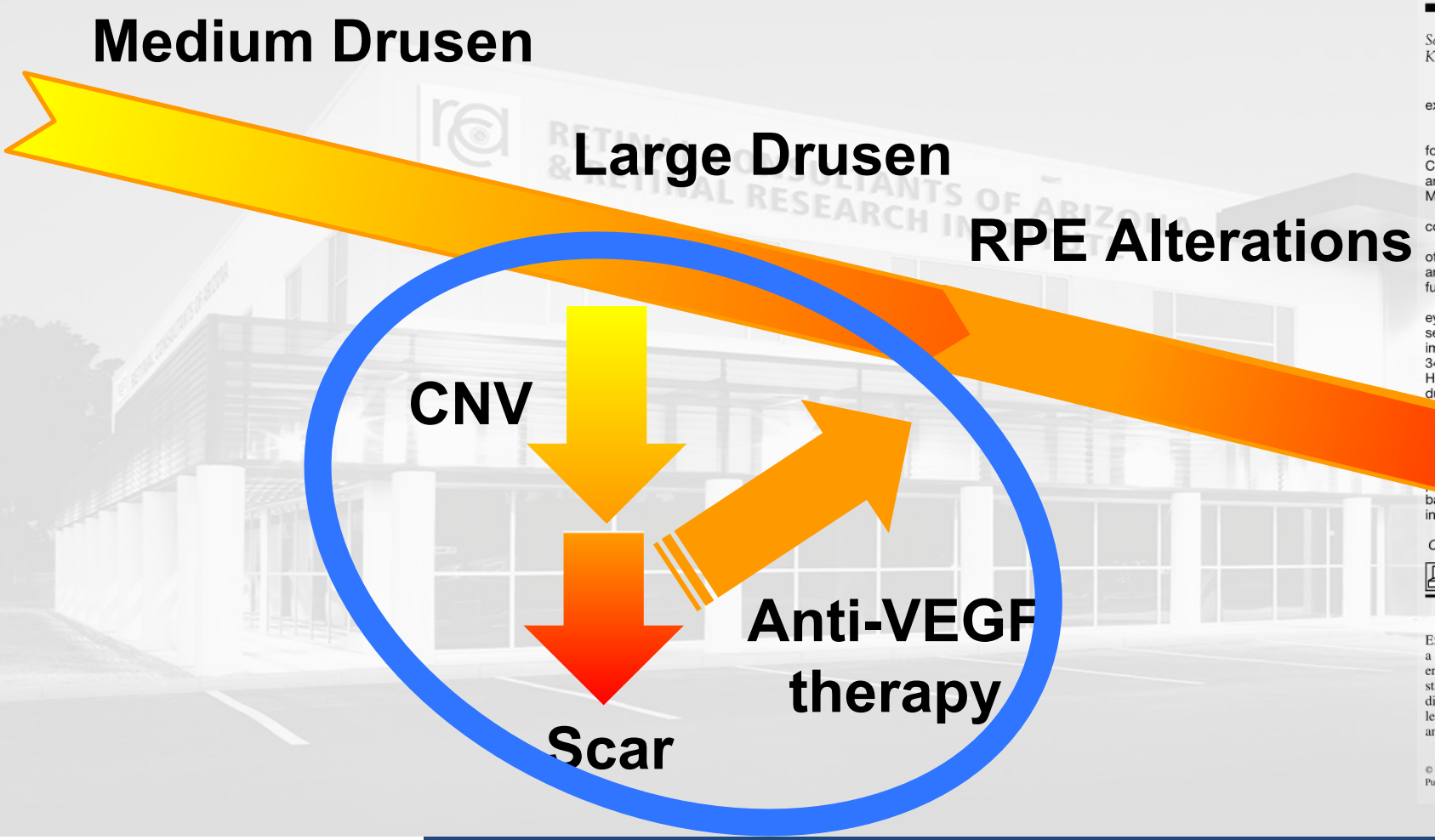
Spectra Eye Institute II
Phoenix, Arizona

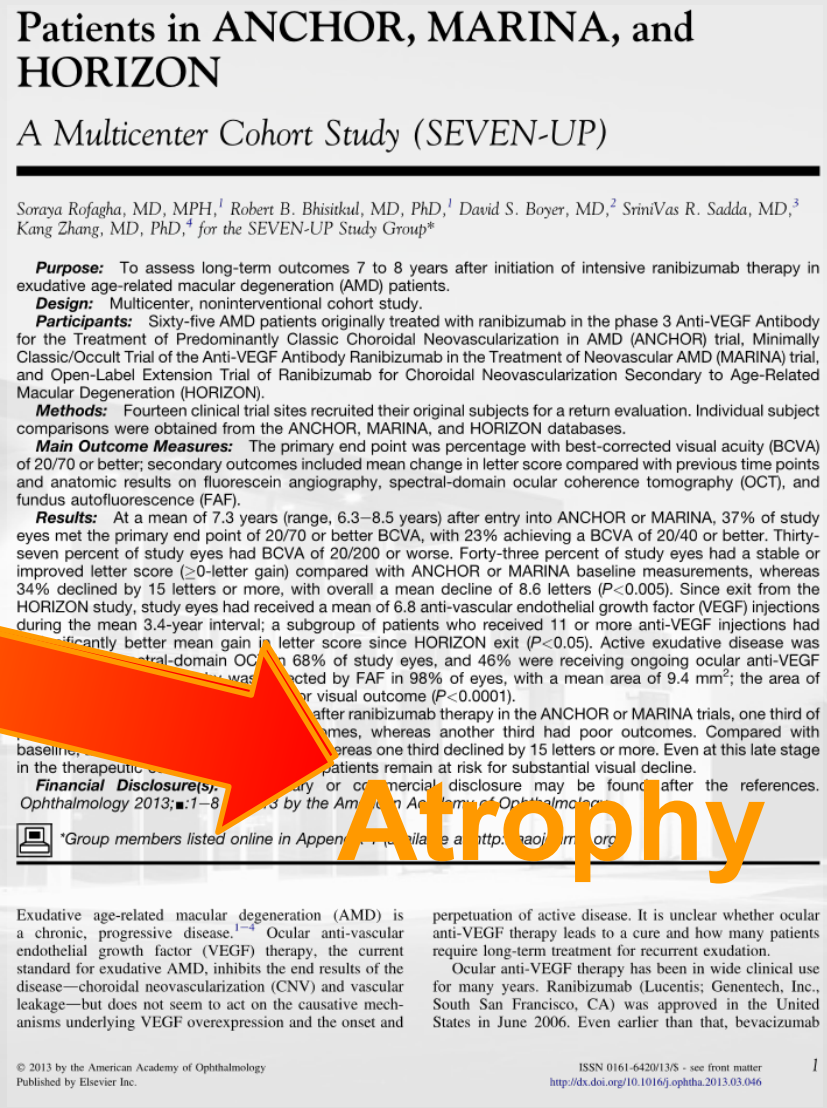
AGE-RELATED MACULAR DEGENERATION (AMD)



Vision Loss with End-Stage Age-Related Macular Degeneration

Pathway of AMD Disease Progression





Patients in ANCHOR, MARINA, and HORIZON

A Multicenter Cohort Study (SEVEN-UP)

*Soraya Rofagha, MD, MPH,[1] Robert B. Bhisitkul, MD, PhD,[1] David S. Boyer, MD,[2] SriniVas R. Sadda, MD,[3] Kang Zhang, MD, PhD,[4] for the SEVEN-UP Study Group**

Purpose: To assess long-term outcomes 7 to 8 years after initiation of intensive ranibizumab therapy in exudative age-related macular degeneration (AMD) patients.

Design: Multicenter, noninterventional cohort study.

Participants: Sixty-five AMD patients originally treated with ranibizumab in the phase 3 Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD (ANCHOR) trial, Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD (MARINA) trial, and Open-Label Extension Trial of Ranibizumab for Choroidal Neovascularization Secondary to Age-Related Macular Degeneration (HORIZON).

Methods: Fourteen clinical trial sites recruited their original subjects for a return evaluation. Individual subject comparisons were obtained from the ANCHOR, MARINA, and HORIZON databases.

Main Outcome Measures: The primary end point was percentage with best-corrected visual acuity (BCVA) of 20/70 or better; secondary outcomes included mean change in letter score compared with previous time points and anatomic results on fluorescein angiography, spectral-domain ocular coherence tomography (OCT), and fundus autofluorescence (FAF).

Results: At a mean of 7.3 years (range, 6.3–8.5 years) after entry into ANCHOR or MARINA, 37% of study eyes met the primary end point of 20/70 or better BCVA, with 23% achieving a BCVA of 20/40 or better. Thirty-seven percent of study eyes had BCVA of 20/200 or worse. Forty-three percent of study eyes had a stable or improved letter score (≥0-letter gain) compared with ANCHOR or MARINA baseline measurements, whereas 34% declined by 15 letters or more, with overall a mean decline of 8.6 letters ($P<0.005$). Since exit from the HORIZON study, study eyes had received a mean of 6.8 anti-vascular endothelial growth factor (VEGF) injections during the mean 3.4-year interval; a subgroup of patients who received 11 or more anti-VEGF injections had [illegible]ificantly better mean gain in letter score since HORIZON exit ($P<0.05$). Active exudative disease was [illegible]tral-domain OC[illegible] 68% of study eyes, and 46% were receiving ongoing ocular anti-VEGF [illegible] was [illegible]cted by FAF in 98% of eyes, with a mean area of 9.4 mm^2; the area of [illegible] visual outcome ($P<0.0001$).

[illegible] after ranibizumab therapy in the ANCHOR or MARINA trials, one third of [illegible]mes, whereas another third had poor outcomes. Compared with baseline, [illegible]ereas one third declined by 15 letters or more. Even at this late stage in the therapeutic [illegible] patients remain at risk for substantial visual decline.

Financial Disclosure(s): [illegible]ary or commercial disclosure may be found after the references.

Ophthalmology 2013;■:1–8 [illegible]3 by the Am[illegible] Ac[illegible] of Ophthalmology

**Group members listed online in Appen[illegible] a[illegible] http:[illegible]aoi[illegible]org*

Exudative age-related macular degeneration (AMD) is a chronic, progressive disease.[1–4] Ocular anti-vascular endothelial growth factor (VEGF) therapy, the current standard for exudative AMD, inhibits the end results of the disease—choroidal neovascularization (CNV) and vascular leakage—but does not seem to act on the causative mechanisms underlying VEGF overexpression and the onset and perpetuation of active disease. It is unclear whether ocular anti-VEGF therapy leads to a cure and how many patients require long-term treatment for recurrent exudation.

Ocular anti-VEGF therapy has been in wide clinical use for many years. Ranibizumab (Lucentis; Genentech, Inc., South San Francisco, CA) was approved in the United States in June 2006. Even earlier than that, bevacizumab

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http://dx.doi.org/10.1016/j.ophtha.2013.03.046

Atrophy

Retinal Consultants of Arizona — in affiliation with — USC Roski Eye Institute Keck Medicine of USC

Multiple Pathways to Atrophy

Drusen-associated atrophy

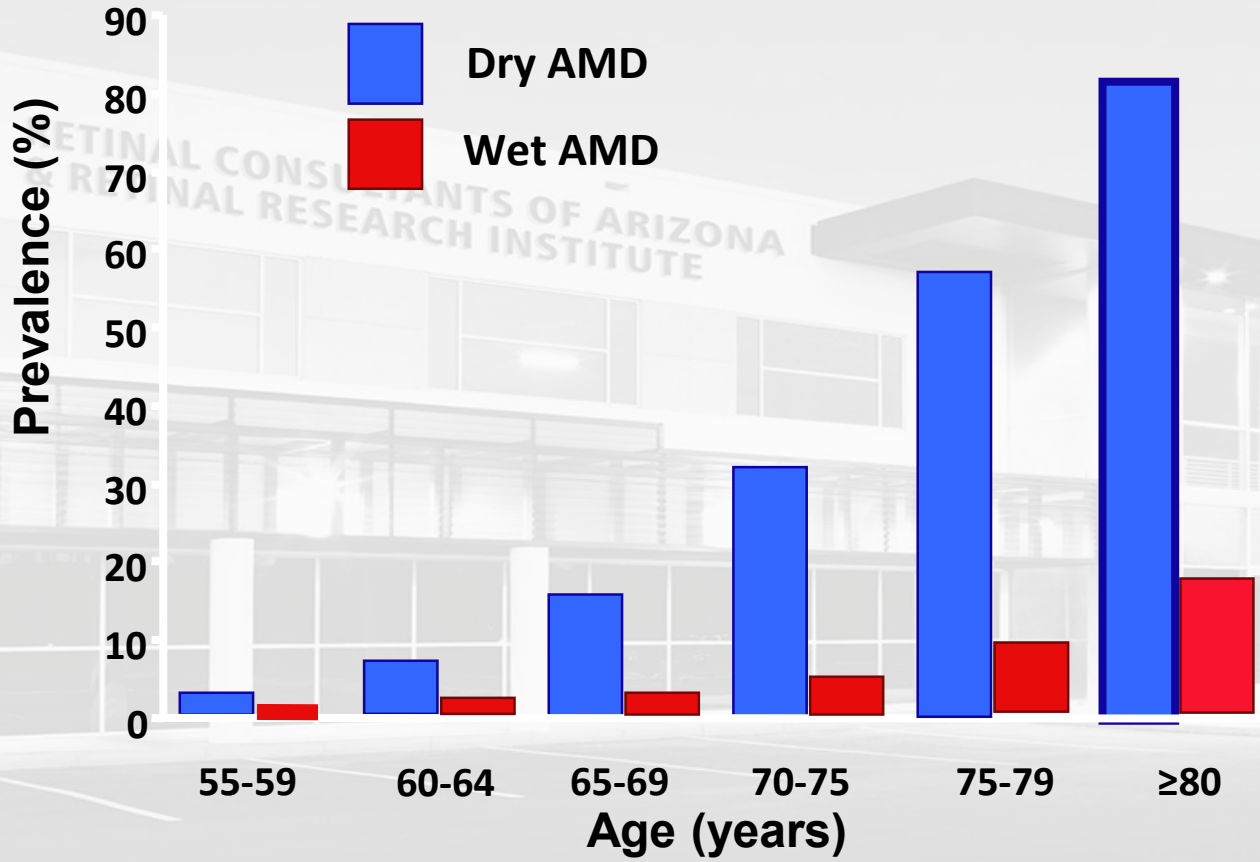
Neovascularization – associated atrophy

Pseudo-drusen associated atrophy

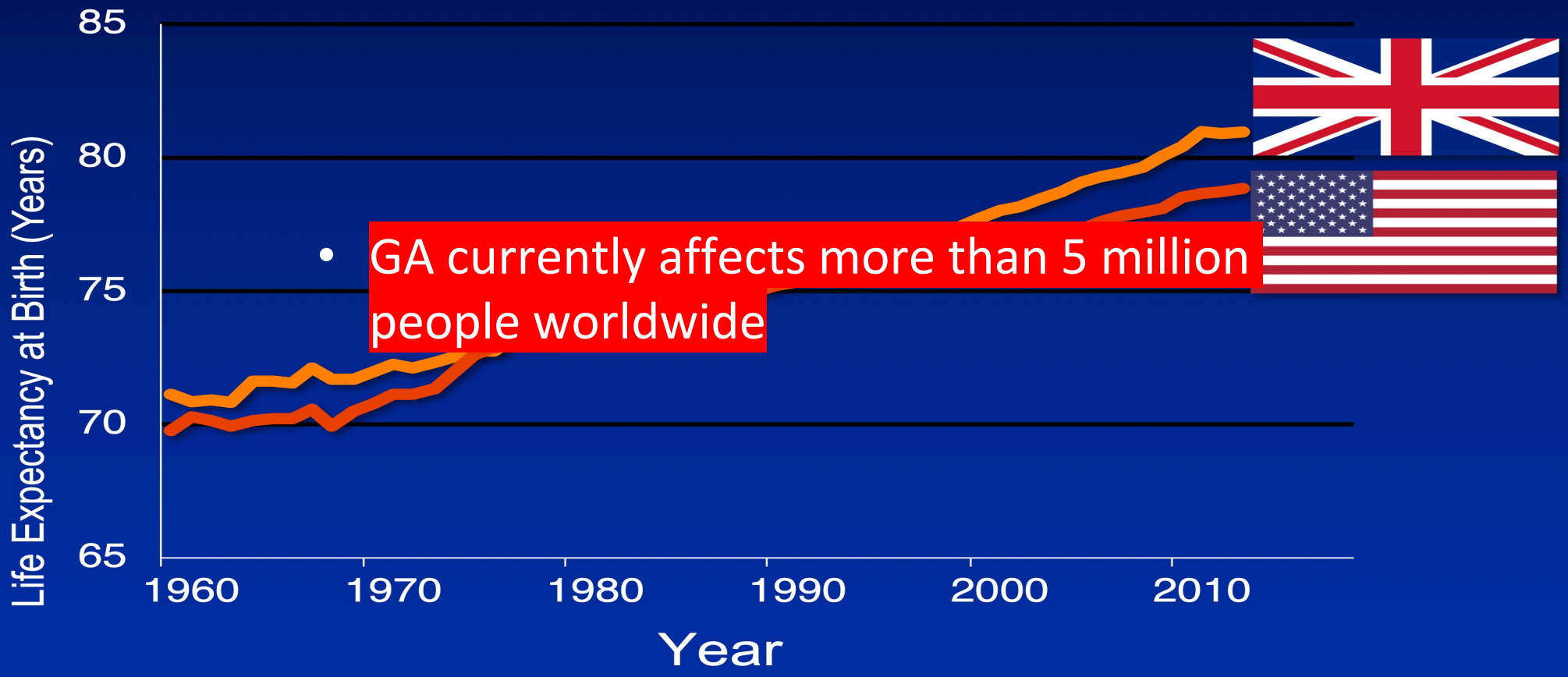
AGE-RELATED MACULAR DEGENERATION

United States: AMD ~15 million people
Prevalence increases with age

Severe vision loss: ~2.0 million people
This population will double by 2030



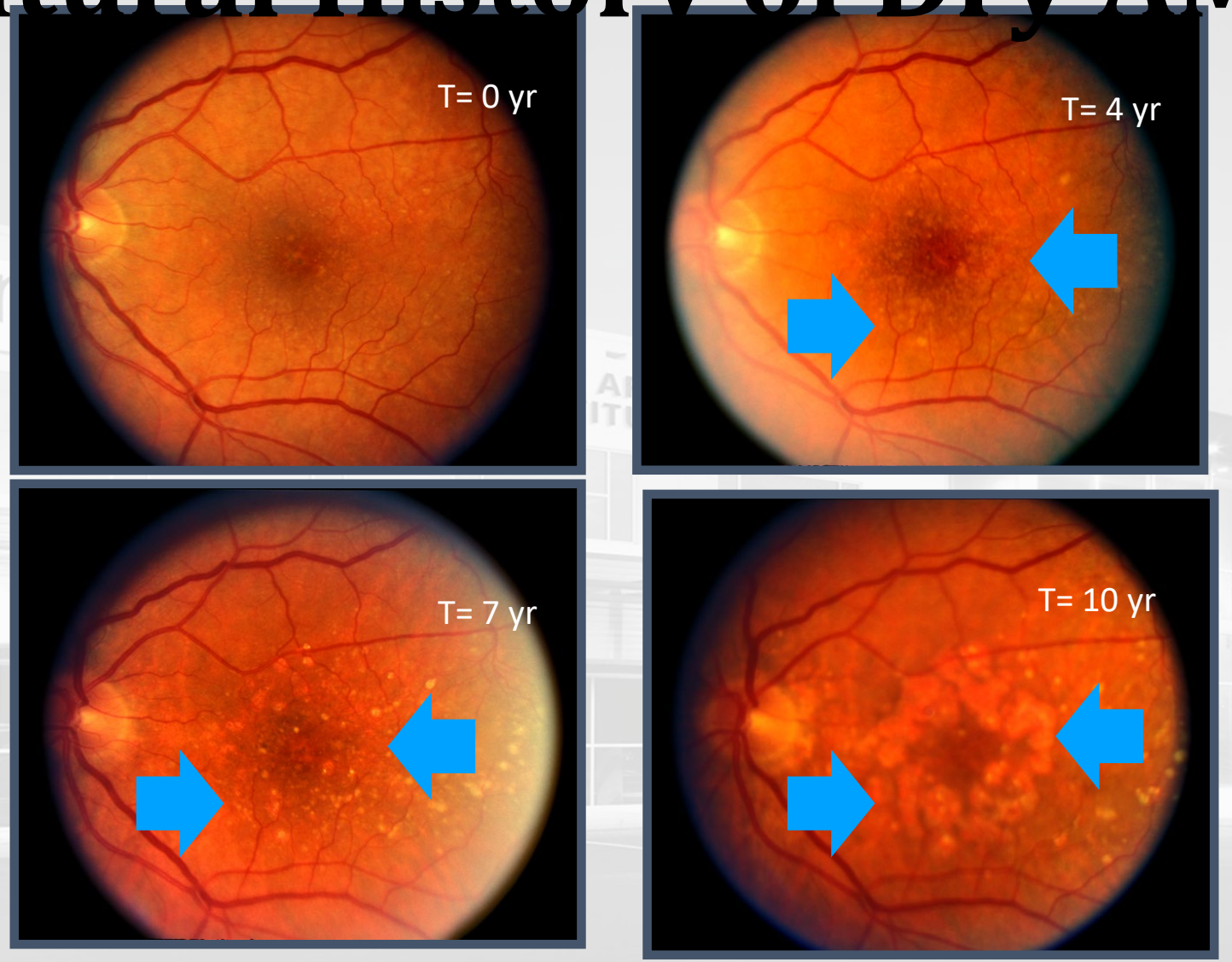
Life expectancies in the US and the UK have risen by ≈10 years since the 1960s[1]



- GA currently affects more than 5 million people worldwide

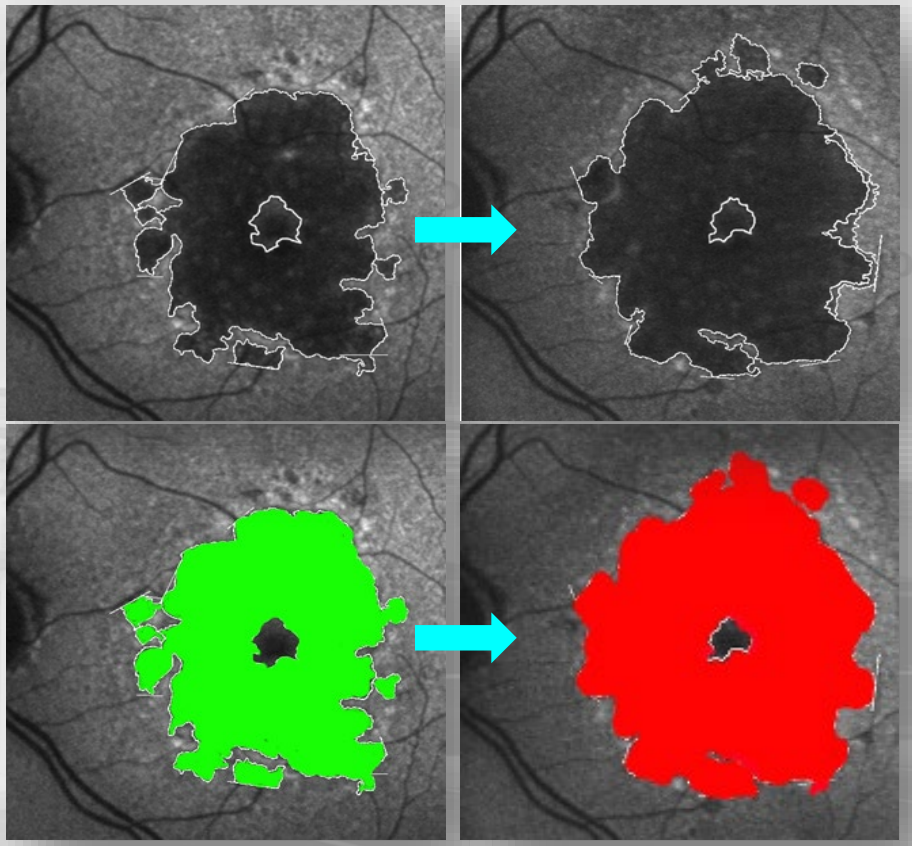
1. http://api.worldbank.org/v2/en/indicator/sp.dyn.le00.in?downloadformat=excel. Accessed 19 August, 2015.

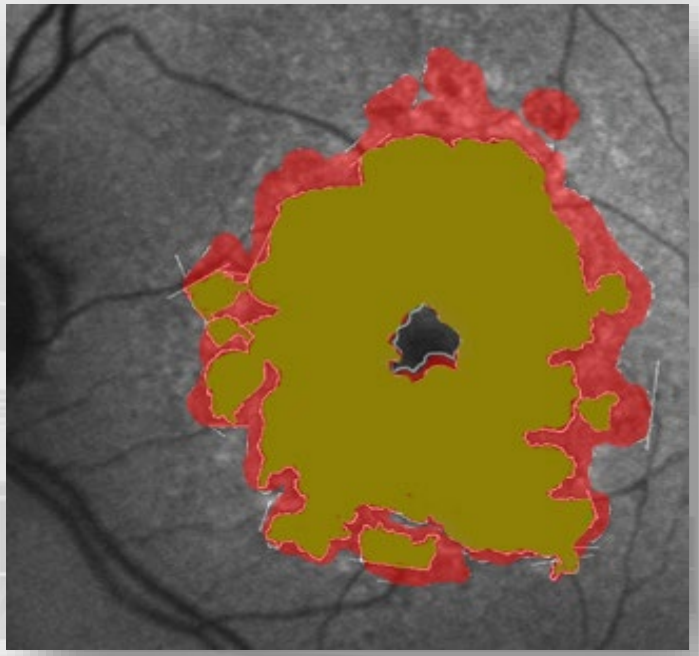
Natural History of Dry AMD



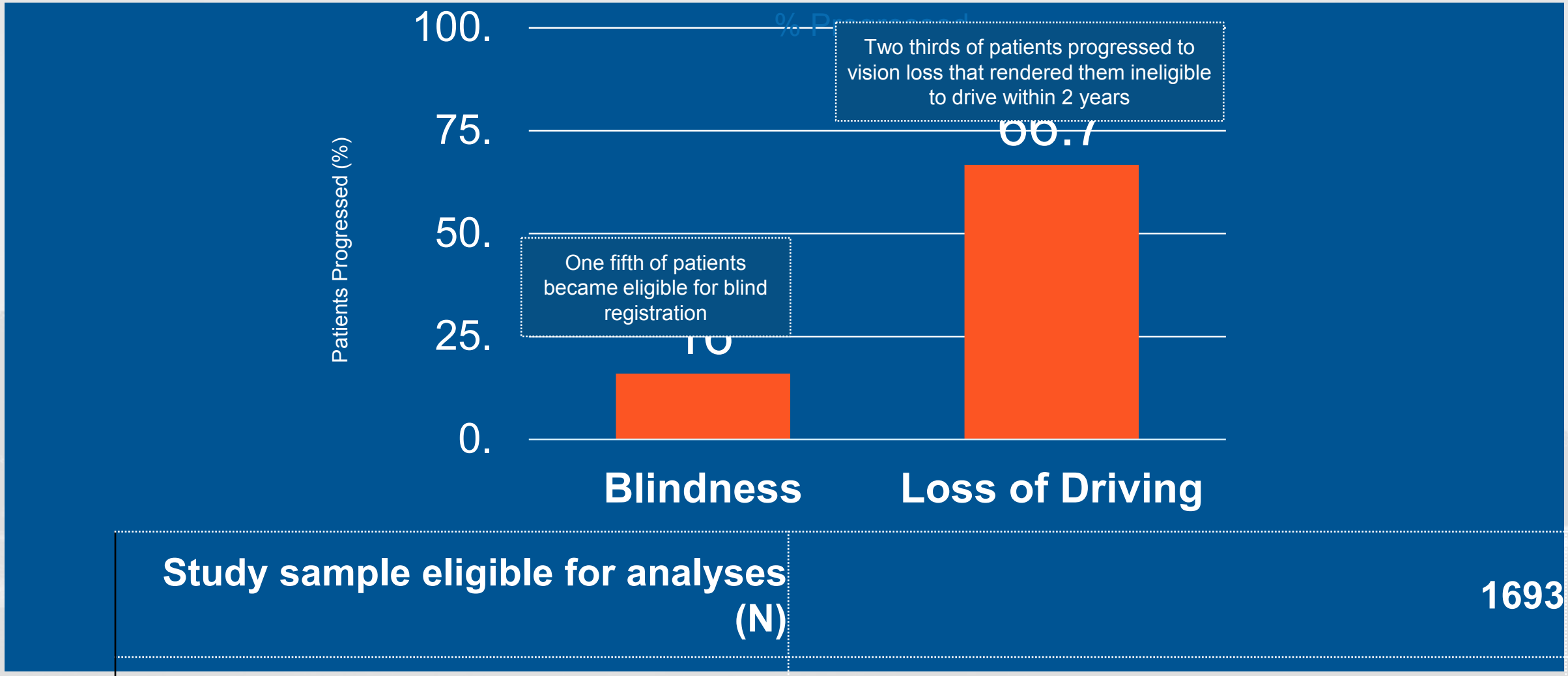
Foveal Sparing

Baseline 40 months f/u





Progression of Vision To Blindness and VA Worse than 20/40 in Better Eye: Bilateral GA Cohort*

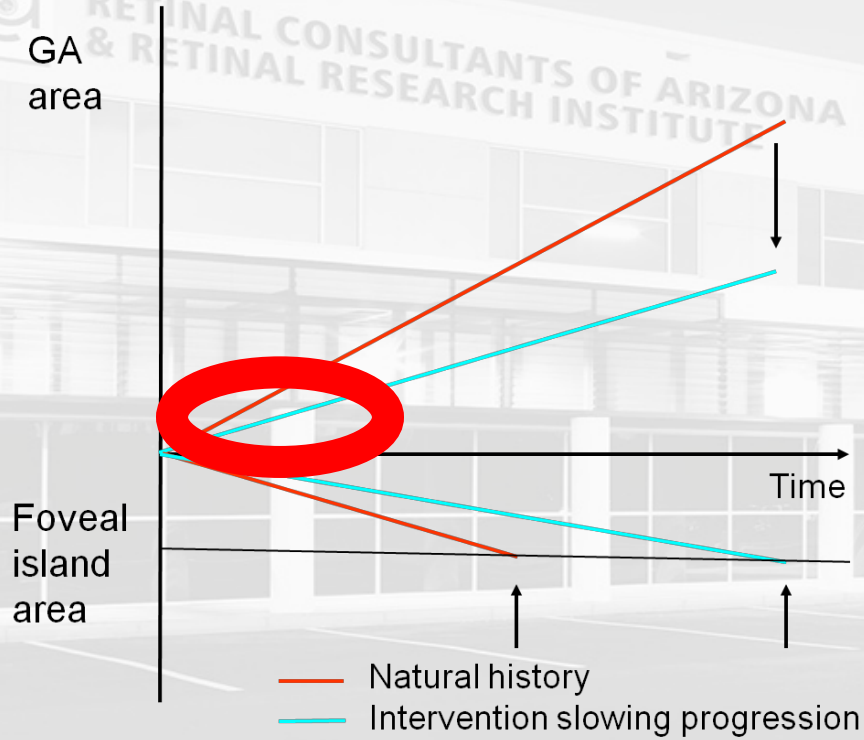


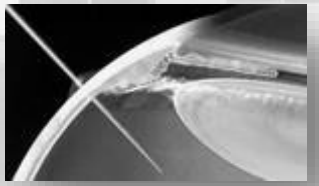
Study sample eligible for analyses (N)	1693
Median (IQR) time to outcome (years)	6.2 (3.3–8.5)

* Results shown previously in All GA Cohorts section; included here for completeness. GA, geographic atrophy; IQR, interquartile range; VA, visual acuity.

Geographic Atrophy
Foveal Sparing‘: Directional kinetics of GA progression

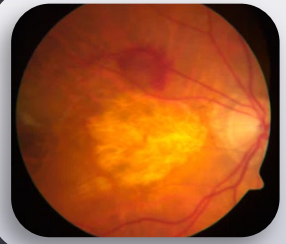
Slowing atrophy growth – clinically relevant?
Avoid additional scotoma - Preserve foveal function





Multiple Pathways to Atrophy

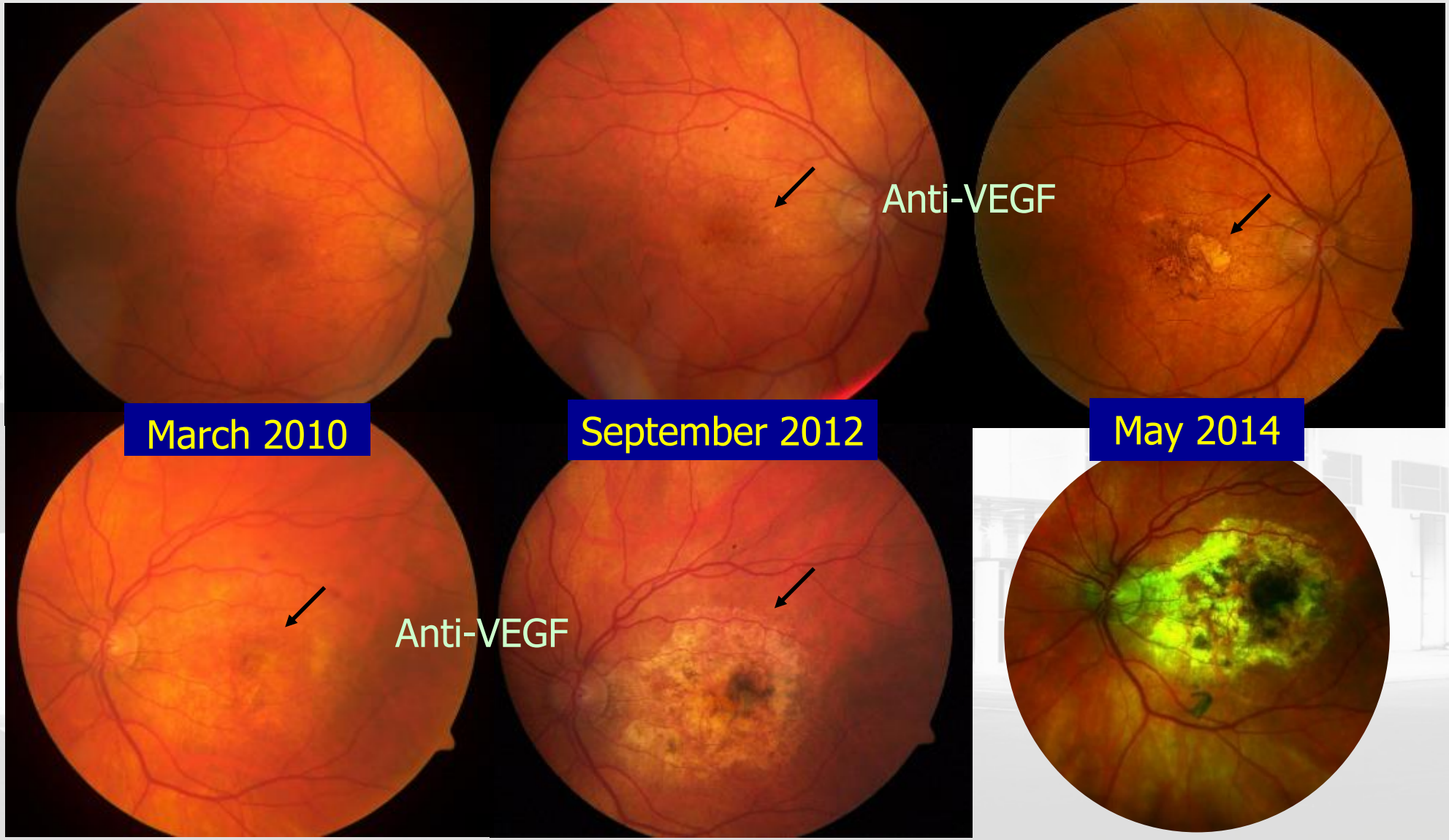
Drusen-associated atrophy



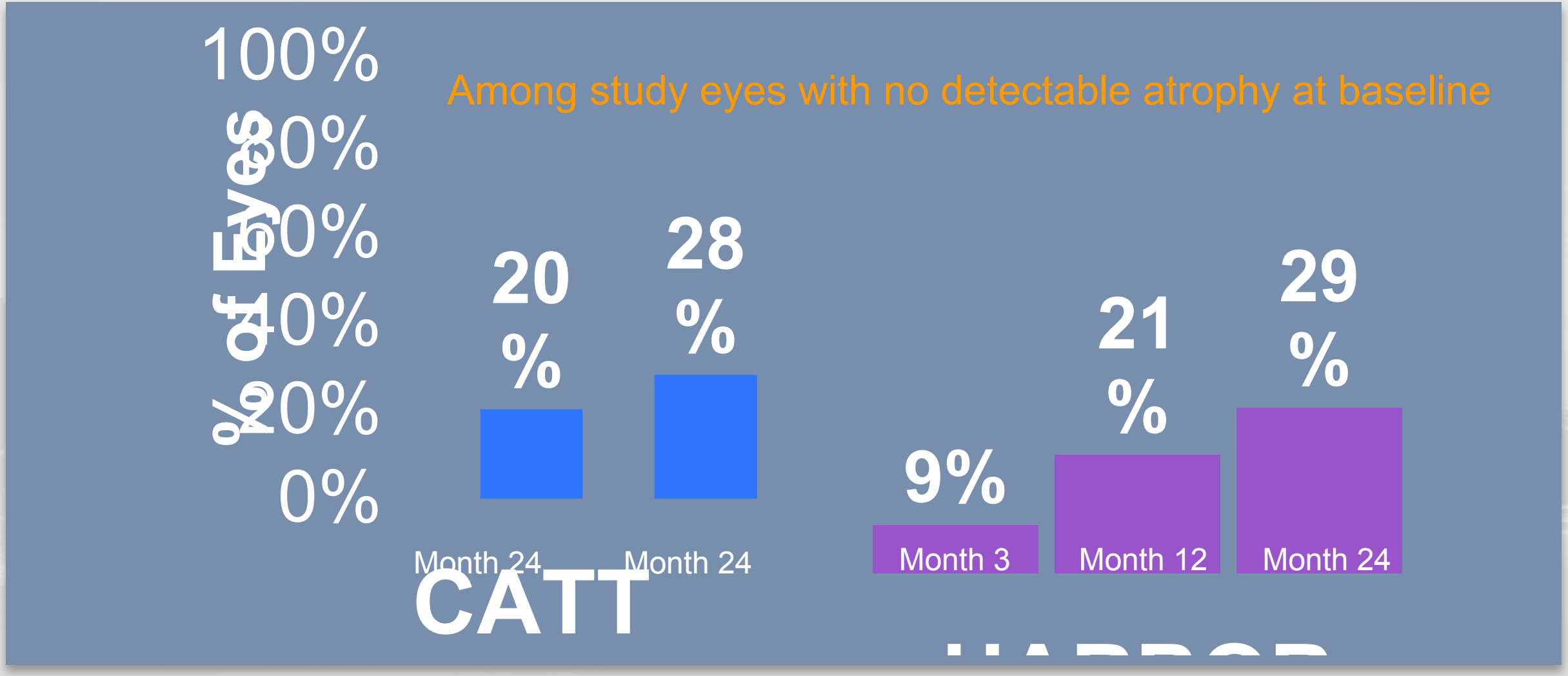
Neovascularization – associated atrophy

Pseudo-drusen associated atrophy

Progression Sequence



Rates of Atrophy in Ranibizumab-Treated Eyes Similar in CATT, IVAN, and HARBOR



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The Journal of Clinical Investigation

RESEARCH ARTICLE

VEGF regulates local inhibitory complement proteins in the eye and kidney

Lindsay S. Keir,[1,2] Rachel Firth,[2] Lyndsey Aponik,[1] Daniel Feitelberg,[1] Susumu Sakimoto,[1] Edith Aguilar,[1] Gavin I. Welsh,[2] Anna Richards,[3] Yoshihiko Usui,[1,4] Simon C. Satchell,[2] Valeryia Kuzmuk,[2] Richard J. Coward,[2] Jonathan Goult,[5] Katherine R. Bull,[5] Ruchi Sharma,[6] Kapil Bharti,[6] Peter D. Westenskow,[1,7] Iacovos P. Michael,[8] Moin A. Saleem,[2] and Martin Friedlander[1]

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VEGF Protects through Modulation of Complement Proteins

Outer retinal and renal glomerular functions rely on specialized vasculature maintained by VEGF that is produced by neighboring epithelial cells, the retinal pigment epithelium (RPE) and podocytes, respectively. Dysregulation of RPE- and podocyte-derived VEGF is associated with neovascularization in wet age-related macular degeneration (AMD), choriocapillaris degeneration, and glomerular thrombotic microangiopathy (TMA). Since complement activation genetic variants in inhibitory complement factor H (CFH) are also features of both AMD and TMA, we hypothesized that VEGF and CFH interact. Here, we demonstrated that VEGF inhibition decreases local CFH and other complement regulators in the eye and kidney through reduced VEGFR2/PKC-α/CREB signaling. Patient podocytes and RPE cells carrying disease-associated CFH genetic variants had more alternative pathway complement deposition than controls. These deposits were increased by VEGF antagonism, a common wet AMD treatment, suggesting that VEGF inhibition could reduce cellular complement regulatory capacity. VEGF antagonism also increased markers of endothelial cell activation, which was partially reduced by genetic complement inhibition. Together, these results suggest that VEGF protects the retinal and glomerular microvasculature, not only through VEGFR2-mediated vasculotrophism, but also through modulation of local complement proteins that could protect against complement-mediated damage. Though further study is warranted, these findings could be relevant for patients receiving VEGF antagonists.

"Together, these results suggest that **VEGF protects the retinal and glomerular microvasculature**, not only through VEGFR2-mediated vasculotrophism, **but also through modulation of local complement proteins that could protect against complement-mediated damage.** Though further study is warranted, these findings could be relevant for patients receiving VEGF antagonists."

J Clin Invest. 2017;127(1):199-214

Intravitreal Anti-VEGF Results in Complement Activation

Aqueous humor from 10 ARMD patient eyes was sampled before and 48 hours after a single intravitreal bevacizumab

J Clin Invest. 2017;127(1):199-214

Complement Inhibition May Protect the Endothelium

ARMD pathogenesis. The most widely studied is the CFH 402H polymorphism, and we demonstrated that RPE cells with this polymorphism showed more cell-surface complement deposition. This supports previous studies that showed CFH 402H does not effectively bind to the cell surface glycosaminoglycan heparan sulphate and this can affect surface complement regulation (24, 41, [illegible]). In the kidney, [illegible] aHUS [illegible] also [illegible] the protein's ability to bind to the cell surface and regulate complement (43). Therefore, we compared an aHUS podocyte cell line with a known CFH mutation (40) to the ARMD RPE cells with the CFH polymorphism in our complement activation assay and obtained similar results, suggesting that the effect observed in RPE cells could be due to impaired cell-surface binding of CFH 402H. Formal binding studies would be needed to confirm these results.

Complement activation is a known feature of ARMD (21, 23, 24, 44), and our experiments suggest VEGF antagonism could exacerbate this by reducing synthesis of CFH and other inhibitory complement proteins. Since both C3 and C4 deposits were increased by VEGF antagonism, these effects likely represent changes in multiple complement inhibitors simultaneously. These effects were more pronounced in cells expressing CFH 402H, possibly because they already have reduced complement regulatory capacity and anti-VEGF treatment could decrease this further. This could explain why the CFH 402H polymorphism has been reported to correlate with a reduced response to anti-VEGF therapy (19, 45, 46), although in this complex disease, it is likely that several other factors also contribute to the variable response to anti-VEGF therapy (47). Furthermore, while controversial, there are patient studies suggesting that VEGF antagonists may enhance progression of GA (8, 9, 48, 49), which could be related to direct complement-mediated damage of the RPE cells. Importantly, this does not affect every patient and more work is needed to identify those at risk, but homozygosity of the CFH 402H polymorphism may be one factor.

Complement activation may also affect the choroidal vasculature (50). Our studies showed that inhibiting complement partially prevented the anti-VEGF-induced increase in endothelial cell activation, suggesting that complement inhibition could protect the endothelium. Previous animal [illegible] showed that alternative pathway activation contributes to the development of CNV (51, [illegible]), which cell culture studies revealed that subcytic levels of MAC can increase RPE-derived VEGF (44), which could contribute to the development of CNV. Considering these data, early complement inhibition in ARMD may prevent some of these negative effects and could reduce the abnormal increase in secreted RPE-derived VEGF. However, a balance must be struck, since murine studies also suggest that complete, prolonged complement inhibition is detrimental (53). Further work is needed to examine this, particularly in humans, since there are important species differences in the complement cascade. Complement inhibition in ARMD, including GA, is an area of active study, with several agents currently in phase 2/3 trials (54).

Complement protein mutations are also associated with glomerular TMA, as shown by studies of familial aHUS (55). The same glomerular pathology was later identified in patients receiving systemic bevacizumab to treat tumor angiogenesis (56, 57). Eremina et al. showed that these effects were replicated in mice with a glomerular-specific VEGF knockout (29), highlighting the importance of local podocyte-derived VEGF in the maintenance of the glomerular endothelium. Using the same model and human cells in vitro, we show that reduced glomerular VEGF decreased expression of local CFH and other complement regulators in both podocytes and glomerular endothelial cells, predisposing them to complement deposition. These findings link the pathogenesis of glomerular TMA associated with anti-VEGF therapy to that of complement-mediated aHUS and may explain why the renal glomerulus is susceptible to complement-mediated disease. Interestingly, preeclampsia, another glomerular disease associated

"Our studies showed that inhibiting complement partially prevented the anti-VEGF–induced increase in endothelial cell activation, suggesting that complement inhibition could protect the endothelium."

"there are patient studies suggesting that VEGF antagonists may enhance progression of GA (8, 9, 48, 49), which could be related to direct complement-mediated damage of the RPE cells."

J Clin Invest. 2017;127(1):199-214

Multiple Pathways to Atrophy

Drusen-associated atrophy

Neovascularization – associated atrophy

Pseudo-drusen associated atrophy

Reticular Pseudodrusen Associated Atrophy

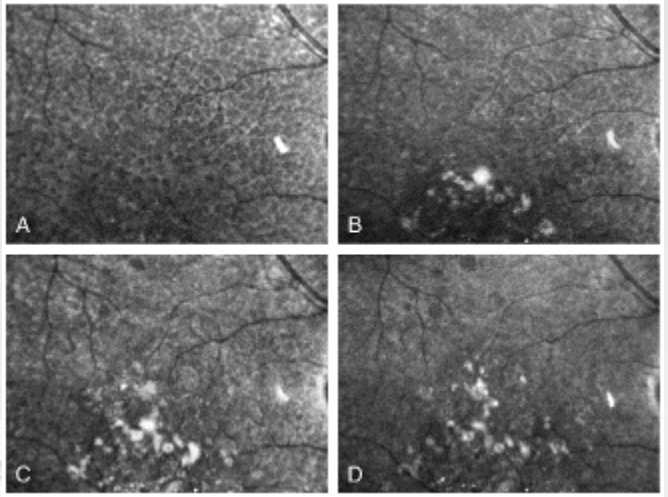
OUTER RETINAL ATROPHY AFTER REGRESSION OF SUBRETINAL DRUSENOID DEPOSITS AS A NEWLY RECOGNIZED FORM OF LATE AGE-RELATED MACULAR DEGENERATION

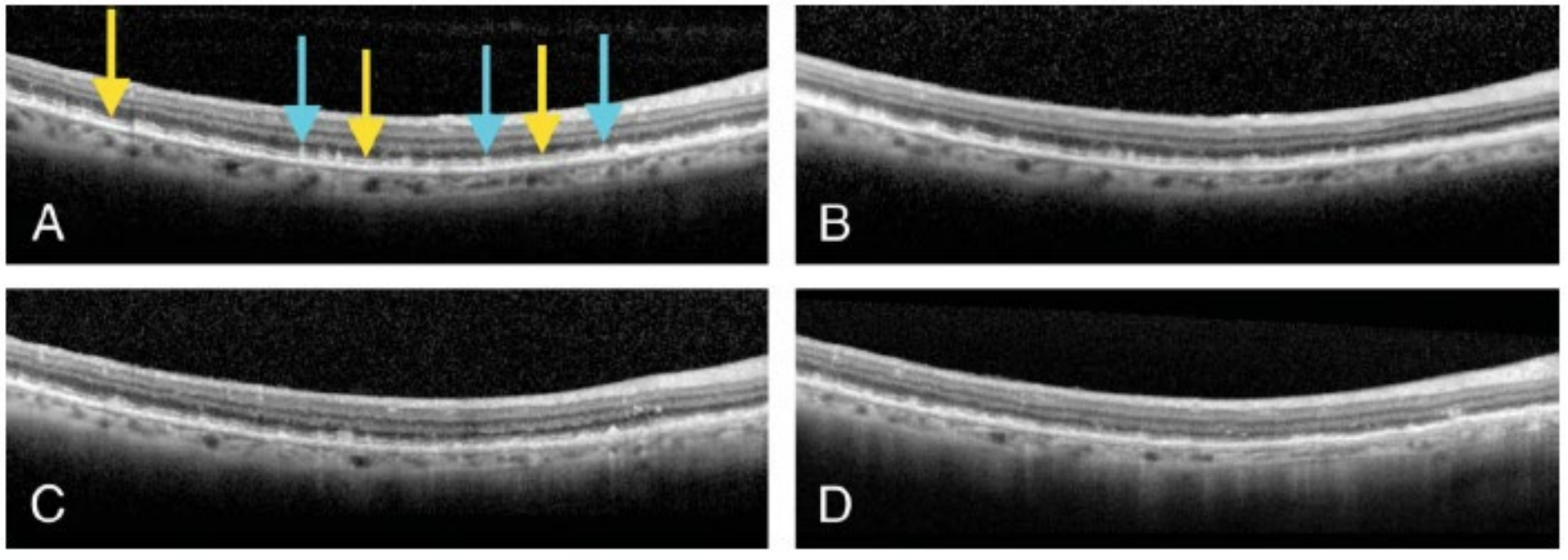
RICHARD F. SPAIDE, MD

Purpose: To investigate the long-term clinical course of eyes with pseudodrusen appearance caused by subretinal drusenoid deposits.

Methods: Eyes from the original study identifying subretinal deposits of material as the cause of pseudodrusen appearance were evaluated in a retrospective study of outer retinal morphology. The distance between the inner plexiform layer and the retinal pigment epithelium, termed the photoreceptor length, was measured from optical coherence tomography approximately 2 mm superior to the fovea at baseline and at follow-up visits. The choroidal thickness was measured directly under this retinal area.

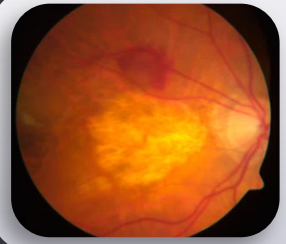
Results: Of the 21 eyes available for follow-up, 9 (42.9%) eventually developed choroidal





Multiple Pathways to Atrophy

Drusen-associated atrophy



Neovascularization – associated atrophy

Pseudo-drusen associated atrophy

Pathway of AMD Disease Progression

Medium Drusen

Large Drusen

RPE Alterations

CNV

Anti-VEGF therapy

Scar

Complement Inhibition

Atrophy

Patients in ANCHOR, MARINA, and HORIZON

A Multicenter Cohort Study (SEVEN-UP)

Exudative age-related macular degeneration (AMD) is a chronic, progressive disease.[1–4] Ocular anti-vascular endothelial growth factor (VEGF) therapy, the current standard for exudative AMD, inhibits the end results of the disease—choroidal neovascularization (CNV) and vascular leakage—but does not seem to act on the causative mechanisms underlying VEGF overexpression and the onset and perpetuation of active disease. It is unclear whether ocular anti-VEGF therapy leads to a cure and how many patients require long-term treatment for recurrent exudation.

Ocular anti-VEGF therapy has been in wide clinical use for many years. Ranibizumab (Lucentis; Genentech, Inc., South San Francisco, CA) was approved in the United States in June 2006. Even earlier than that, bevacizumab

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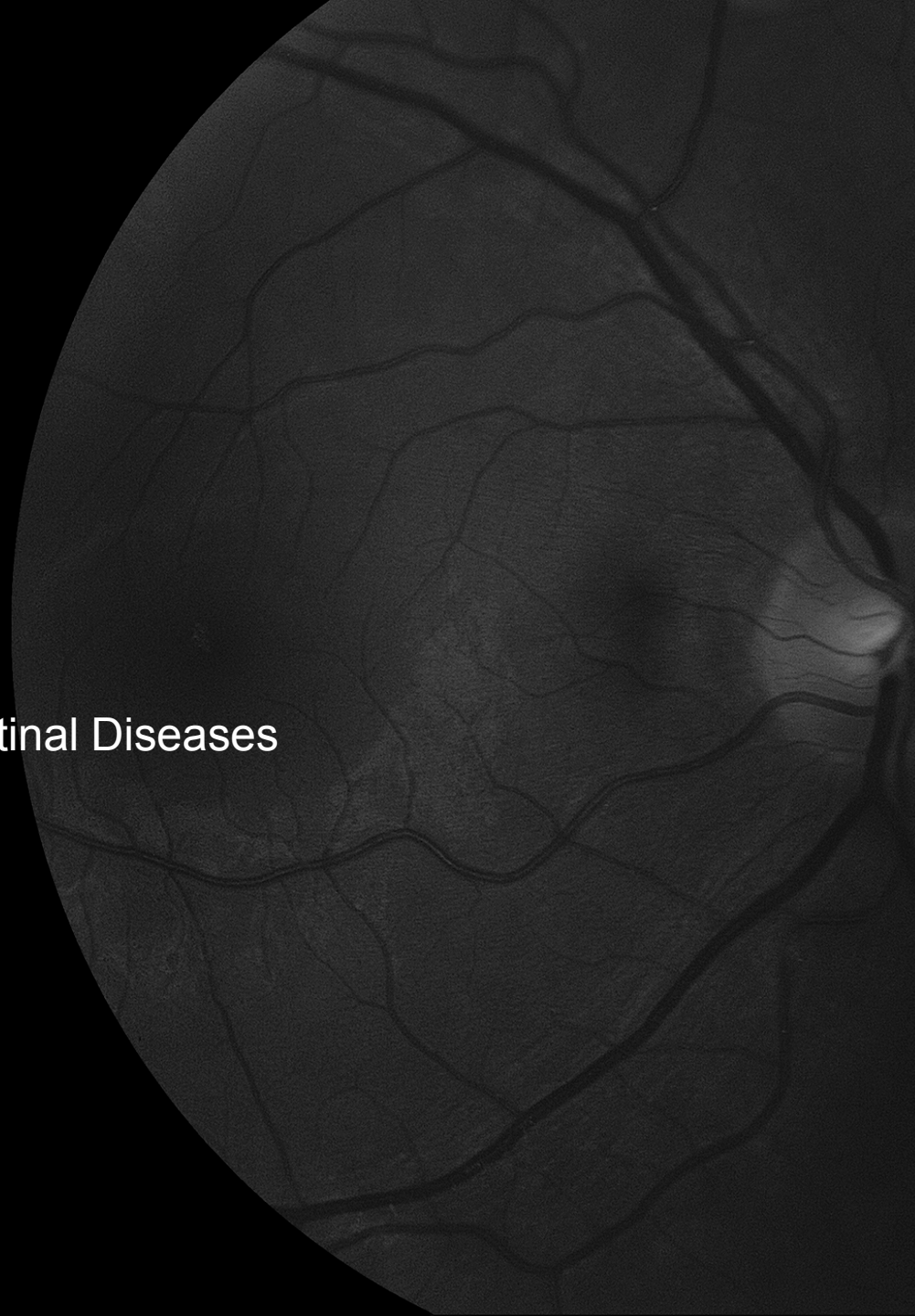
IVERIC bio

Developing Transformative Therapies for Retinal Diseases

Kourous A. Rezaei, MD
Chief Medical Officer



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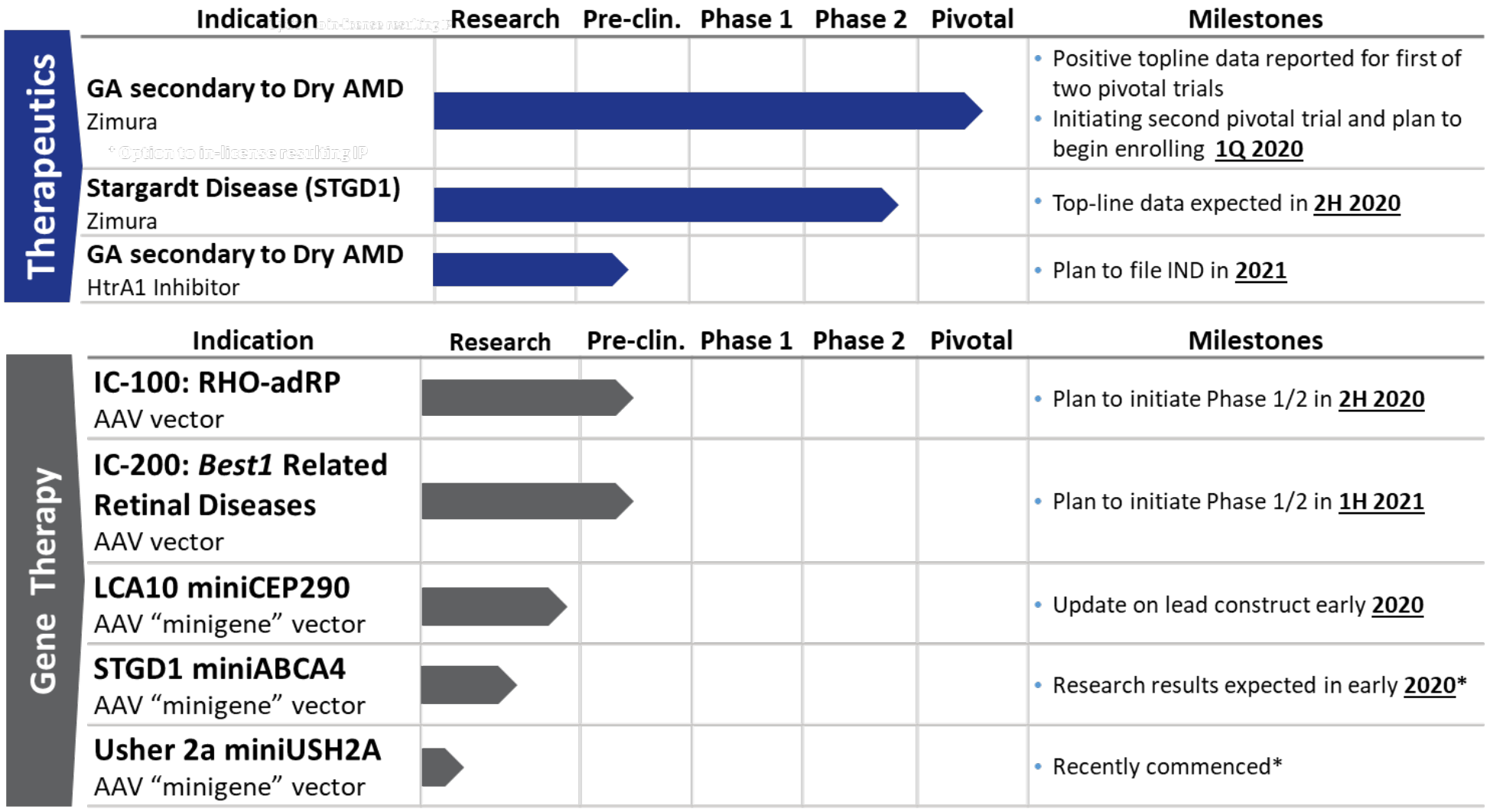

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