Complement C3 Inhibition in Geographic Atrophy

Jason S. Slakter, MD
Clinical Professor of Ophthalmology, NYU School of Medicine
Director Digital Angiography Reading Center
## Agenda

### Introduction

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<thead>
<tr>
<th>Time</th>
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<th>Presenter</th>
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<tr>
<td>10:00 – 10:05 am</td>
<td>Welcome and Introduction to Apellis</td>
<td>Federico Grossi</td>
</tr>
</tbody>
</table>

### Main Session

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
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</tr>
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<tbody>
<tr>
<td>10:05 – 10:20 am</td>
<td>Disease Burden in Geographic Atrophy</td>
<td>Usha Chakravarthy, MD, PhD</td>
</tr>
<tr>
<td>10:20 – 10:35 am</td>
<td>Complement Activation in Geographic Atrophy and APL-2 Mechanism of Action</td>
<td>Phil Rosenfeld, MD, PhD</td>
</tr>
<tr>
<td>10:35 – 10:50 am</td>
<td>FILLY Phase 2 Results and Phase 3 Study Design</td>
<td>Frank Holz, MD</td>
</tr>
<tr>
<td>10:50 – 11:00 am</td>
<td>Panel Discussion</td>
<td>Moderated by Jason Slakter, MD</td>
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</table>
Welcome and Introduction to Apellis

Federico Grossi, MD, PhD
EVP of Clinical Development and Medical Affairs
Data that will be presented today come from a study on the disease burden of GA in the NHS in the UK funded by Roche.
Key Takeaways

GA is a cause of similar levels of visual morbidity as CNV

• Real-world data confirm that GA is a progressive disease and is associated with high levels of visual impairment, with impacts on mobility and independence

• Proportion of eyes progressing to blindness is greater than that recorded in previous clinical studies

• GA and CNV are manifestations of the same disorder with specific temporal relationships
Introduction

• Geographic atrophy (GA) is an advanced form of age-related macular degeneration (AMD) characterised by progressive and irreversible loss of the retinal pigment epithelium (RPE), photoreceptors and underlying choriocapillaris\(^1,2\)

• Patients experience visual function abnormalities, such as difficulty with reading and seeing in low-light conditions

• Major cause of legal blindness: \(~26\%\) in UK, \(~20\%\) in North America

• No approved treatment available\(^2\)

Prevalence and Incidence of GA

- GA affects >5 million people worldwide\textsuperscript{10}
- Variable prevalence reported in the different studies\textsuperscript{10,11}
  - Particularly when photographic grading has not been used
- GA prevalence
  - Quadruples per decade increase in age ≥50 years\textsuperscript{11}
- A meta-analysis estimated annual incidence of GA at 1.6 cases per 1000, equivalent to 160,000 new cases per year\textsuperscript{18}

GA is also responsible for sight loss in patients with wet AMD despite treatment with anti-VEGF.
Rationale for UK EMR study

• Recent evidence suggesting that GA is the default pathway in AMD
• Increasing awareness that early forms of GA may be more common than previously recognised
• The extent of visual impact of GA may have been underestimated
  – The frequency of severe visual impairment /blindness arising from GA
  – The severity of visual impairment and consequent handicap due to GA
# The UK EMR AMD Study

## Study Design
- Retrospective analysis of a clinical dataset
- Study plan and aims defined prior to data cut
- EMR contains prospectively defined data fields (similar to electronic case report forms used in clinical trials rather than a retrospective chart review)

## Data Source
- Medisoft EMR

## Site Selection
- 10 NHS retina clinics contributed to the study

## Period Covered
- Data cut made in Feb 2016 (period covered Oct 2000–Feb 2016)
- Periods of EMR usage varied by centre as not all centres implemented EMR at the same time

AMD, age-related macular degeneration; EMR, electronic medical record; NHS, National Health Service. UK EMR GA study Chakravarthy et al Ophthalmology
Study Population – GA Cohorts

Anonymised data from 83,425 patients (diagnosis of any AMD) 10 UK retinal centres between 2000 and 2016

Cases with at least 1 eye with a clinical record of GA recorded at any visit N = 11,240 (13.5%)

Main Exclusions:
- Age at index <50 years
- CNV in both eyes at index date
- Study eye with <30 days’ follow-up
- No information for the fellow eye in the EMR system, or fellow eye is not classifiable
- Missing VA data ±90 days of index date

Disease definition

Eligible GA cohort - 4769 (5.7%)

- GA:GA 1901 (39.9%)
  - Both study and fellow eye with GA
- GA:CNV 1696 (35.6%)
  - Study eye with GA; fellow eye with CNV
- GA:Early AMD 1172 (24.6%)
  - Study eye with GA; fellow eye with Early/Intermediate AMD

AMD, age-related macular degeneration; CNV, choroidal neovascularisation; EMR, electronic medical record; GA, geographic atrophy; VA, visual acuity.
Among patients who did not meet the VA criteria for blindness at baseline, defined as <20 VA letters or Snellen 3/60 in better-seeing eye (US Snellen ~20/400). AMD, age-related macular degeneration; CNV, choroidal neovascularisation; GA, geographic atrophy; VA, visual acuity.
Percentage of Patients who Became Ineligible to Drive in the UK During Follow Up

Among patients who did not meet the VA criteria for eligibility to drive at baseline, defined as better-seeing eye of >70 letters or Snellen 6/12 (US Snellen ~20/40). AMD, age-related macular degeneration; CNV, choroidal neovascularisation; GA, geographic atrophy; VA, visual acuity.
Outcome Measures: Bilateral GA Cohort

**GA:GA Cohort**

<table>
<thead>
<tr>
<th>Populations Analysed</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td>GA:GA ALL 1901</td>
<td>• Progression to CNV</td>
</tr>
<tr>
<td></td>
<td>• Progression to blindness</td>
</tr>
<tr>
<td></td>
<td>• Loss of ≥10 letters of VA</td>
</tr>
<tr>
<td></td>
<td>• Progression to loss of eligibility to drive</td>
</tr>
<tr>
<td>Did not meet definition of UK blindness at baseline* 1693</td>
<td>• Progression to blindness</td>
</tr>
<tr>
<td></td>
<td>• Loss of ≥15 letters of VA</td>
</tr>
<tr>
<td>Eligible to drive at baseline† (UK standard) 523</td>
<td>• Progression to loss of eligibility to drive</td>
</tr>
</tbody>
</table>

*Blindness definition (UK): VA measurement of <20 ETDRS letters or Snellen 3/60 in the better-seeing eye.
†Driving eligibility standard (UK): VA measurement in better-seeing eye of >70 letters or Snellen 6/12.
CNV, choroidal neovascularisation; ETDRS, Early Treatment Diabetic Retinopathy Study; GA, geographic atrophy; VA, visual acuity.
Progression to CNV and VA Loss: Bilateral GA Cohort

<table>
<thead>
<tr>
<th>Study sample eligible for analyses (N)</th>
<th>1901</th>
<th>1693</th>
<th>1693</th>
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</thead>
<tbody>
<tr>
<td>Median (IQR) time to outcome (years)</td>
<td>1.1</td>
<td>3.3</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>(0.3–2.0)</td>
<td>(1.5–6.2)</td>
<td>(1.1–5.0)</td>
</tr>
</tbody>
</table>

One third of patients lost 15 letters/3 lines of VA

40% of patients lost 10 letters/2 lines of VA

8% CNV

31% Loss of ≥15 Letters

40% Loss of ≥10 Letters

0
10
20
30
40
50
60
70
Patients Progressed (%)

Loss of ≥15 Letters

Loss of ≥10 Letters
Change in Mean VA from Baseline in Better-Seeing and Worse-Seeing Eyes Over Time: Bilateral GA Cohort

For each time point, patients had to have VA measurement at index and at the specific time point of 12, 24 or 60 months post index. For the better-seeing eye, the sample comprised 726, 414 and 80 patients for the 12, 24 and 60 time points, respectively. For the worse-seeing eye, the sample comprised 724, 413 and 80 patients for the 12, 24 and 60 time points, respectively.

ETDRS, Early Treatment Diabetic Retinopathy Study; VA, visual acuity.

For each time point, patients had to have VA measurement at index and at the specific time point of 12, 24 or 60 months post index. For the better-seeing eye, the sample comprised 726, 414 and 80 patients for the 12, 24 and 60 time points, respectively. For the worse-seeing-eye, the sample comprised 724, 413 and 80 patients for the 12, 24 and 60 time points, respectively. ETDRS, Early Treatment Diabetic Retinopathy Study; VA, visual acuity.
Progression of Vision To Blindness and VA Worse than 20/40 in Better Eye: Bilateral GA Cohort*

One fifth of patients became eligible for blind registration

Two thirds of patients progressed to vision loss that rendered them ineligible to drive within 2 years

Study sample eligible for analyses (N) | 1693 | 523
--- | ---
Median (IQR) time to outcome (years) | 6.2 (3.3–8.5) | 1.6 (0.7–2.7)

* Results shown previously in All GA Cohorts section; included here for completeness. GA, geographic atrophy; IQR, interquartile range; VA, visual acuity.
Visual Acuity may not reflect the true impact of GA

<table>
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<tr>
<th>Baseline 20/63</th>
<th>2.3 years 20/63</th>
<th>4.0 years 20/63</th>
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<tr>
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<td><img src="image3" alt="Image" /></td>
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<th>Baseline 20/63</th>
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<th>4.3 years 20/200</th>
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<td><img src="image5" alt="Image" /></td>
<td><img src="image6" alt="Image" /></td>
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Courtesy of Frank Holz
Good distance VA does not mean that reading ability is maintained.
Key Takeaways

GA is a cause of similar levels of visual morbidity as CNV

• Real-world data confirm that GA is a progressive disease and is associated with high levels of visual impairment, with impacts on mobility and independence

• Proportion of eyes progressing to blindness is greater than that recorded in previous clinical studies

• GA and CNV are manifestations of the same disorder with specific temporal relationships
Complement Activation in Geographic Atrophy and APL-2 Mechanism of Action

Complement C3 Inhibition in Geographic Atrophy Symposium
18th EURETINA CONGRESS, Vienna, Austria
September 22, 2018

Philip J. Rosenfeld, MD, PhD
Professor of Ophthalmology
Bascom Palmer Eye Institute
University of Miami Miller School of Medicine
Disclosures

Financial interests or relationships:

- Acucela: Consultant
- Apellis: Consultant, Equity ownership
- Boehringer-Ingelheim: Consultant
- Carl Zeiss Meditec: Research Grant/Consultant
- Chengdu Kanghong Biotech: Consultant
- Digisight: Equity ownership
- Genentech: Research grant/Consultant
- Healios K.K.: Consultant
- Hemera Biosciences: Consultant
- Isarna Pharmaceuticals: Consultant
- Lin Bioscience: Consultant
- NGM Biopharmaceuticals: Consultant
- Ocudyne: Consultant, Equity ownership
- Ocunexus Therapeutics: Consultant
- Unity Biotechnology: Consultant
Genetic and histopathologic data strongly suggest an important role for complement activation in AMD

The best target for complement inhibition is unknown, but clinical trial failures have eliminated some targets

POT-4/APL-2 inhibition of C3 provides the best opportunity to inhibit all complement activation

The best stage of AMD to study is unknown, but inhibiting the growth of GA is an accepted regulatory endpoint
Patients with complement-mediated systemic (renal) diseases have macular drusen, and drusen are a hallmark of AMD.

- Complement proteins deposited in drusen, Bruch’s membrane, and the inner choroid in AMD eyes.
- Genetics strongly supports an important role for complement in AMD.
Drusen in Dense Deposit Disease (Membranoproliferative Glomerulonephritis Type II)
Mutation in Complement Factor H
Drusen in C3 Glomerulonephritis (Idiopathic Glomerulonephritis)

Mutations in Complement C3

Patients with complement-mediated systemic (renal) diseases have macular drusen, and drusen are a hallmark of AMD.

- Complement proteins deposited in drusen, Bruch’s membrane, and the inner choroid in AMD eyes.
- Genetics strongly supports an important role for complement in AMD.
Location of Complement Proteins

- **Drusen**
- **Geographic Atrophy**
- **RPE/Bruch's Membrane**
- **Photoreceptors**
- **RPE**
- **Choroid**
Complement in Human Eyes

- Histopathological studies of AMD eyes

C5 staining (RED) of sub-RPE space & drusen”

Complement in Human Eyes

- Histopathological studies of human eyes

Complement C3 (Green) and Lipofuscin (Red)

Localization of complement C3 in human RPE, choroid (CHOR), and neural retina by confocal immunofluorescence microscopy. A and B. C3 immunoreactivity is concentrated in the RPE and choroid, but absent in the photoreceptor layer (PR) of the neural retina (CY2, green). Lipofuscin autofluorescence (CY3, red).

Complement in Human Eyes

- Histopathological studies of human eyes

Factor B (Green) and C5b-9, MAC (Red)

Factor B (green)
MAC (red)

CHOROID
RPE

MAC
Dr

Factor B/C5b-9 co-localization [anti-Factor B (CY2, green); anti-C5b-9 (CY3, red)]. Diffuse anti-Factor B labeling is present throughout the choroid; choroidal capillary vessel walls are heavily labeled (arrowhead). Factor B immunofluorescence can be localized to the cores of some drusen (Dr).

Terminal complement complex in human donor eyes

CHOROID

Membrane Attack Complex (Green)

RPE

C5b-9 terminal complement complex antibody
UEA-I vascular marker

Courtesy of Robert Mullins, University of Iowa
Complement in Human Eyes

- Histopathological studies of human eyes

Factor H (Green) and C-Reactive Protein (Red)

Factor H is localized to choroidal capillaries and the intercapillary pillars (arrowhead) (CY2; green). Lipofuscin autofluorescence (CY5; blue), C-reactive protein (CY3; red)

Patients with complement-mediated systemic (renal) diseases have macular drusen and drusen are a hallmark of AMD.

Complement proteins deposited in drusen, Bruch’s membrane, and the inner choroid in AMD eyes.

Genetics strongly supports an important role for complement in AMD.
**Classical Pathway**
Antigen-Antibody complexes

**Lectin Pathway**
(Mannose sugar residues)

**Alternative Pathway**
(Microbial/Nonspecific Activators)

- C1 Inhibitor
- C1
- MBL
- MASP
- C4
- Factor I
- C2
- Factor B
- Properdin
- Factor D
- Factor H
- C3, C3b
- Factor I
- CFHR1
- CFHR3
- C5a
- C5b
- C6, C7, C8, C9
- C5b-9

Membrane Attack Complex
(lysis and cytotoxicity)
Genetic loci associated with AMD

Membrane Attack Complex (lysis and cytotoxicity)
What About the ARMS2/HTRA1 Locus?

- CFH and ARMS2/HTRA1 are the strongest genetic loci associated with AMD
- What’s the role of the ARMS2*/HTRA1 gene locus?
- Best evidence:
  - HTRA1: Multifunctional serine protease
  - ARMS2*: Unknown, but possibly involved in complement-mediated opsonization of apoptotic and necrotic cells


Complement Inhibition for AMD: What’s the best study design?

- Best clinical trial endpoint?
- Best complement target?
- Best dose?
- Best dosing interval?
- Best route for drug delivery?
Complement Inhibition for AMD: What’s the best study design?

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Non-Exudative AMD Anatomic Clinical Trial Endpoints: Prevent Disease Progression

Anatomic Clinical Trial Endpoints for Nonexudative Age-Related Macular Degeneration

Karen B. Schaal, MD, Philip J. Rosenfeld, MD, PhD, Giovanni Gregori, PhD, Zohar Yehoshua, MD, MHA, William J. Feuer, MS

Topic: To review the role of anatomic endpoints in clinical trials for the study of nonexudative age-related macular degeneration (AMD) with an emphasis on a novel composite endpoint for the study of emerging therapies for intermediate AMD (iAMD).

Clinical Relevance: Unlike clinical trials for exudative AMD, it is impractical to use the change in visual acuity (VA) as a primary endpoint for the study of nonexudative AMD. By the time VA has been lost in nonexudative AMD, proof-of-concept early-stage clinical trials would take years to run, and drug development would be a near impossible task. Surrogate endpoints are needed that reliably predict future vision loss and can be easily measured. Anatomic changes that correlate with disease progression in nonexudative AMD offer the greatest promise as primary endpoints.

Methods: In preparation for this review, the electronic PubMed database was searched for relevant research pertaining to anatomic endpoints for the study of nonexudative AMD. Paper selection was based on our knowledge of the field with the goal to be as inclusive as possible. Whenever possible, recent review articles and results from large clinical trials, preferably with outcomes from many years of follow-up were favored over trials of short duration.

Results: The most commonly used anatomic endpoint for the study of late, nonexudative AMD is the growth of geographic atrophy (GA). The advantages of studying GA include the appreciation that its enlargement through the foveal center leads to significant vision loss through the availability of natural history studies, the understanding that prevention of this growth would preserve vision in the future, the ability to reliably measure GA using different imaging strategies, and the development appropriate statistical tools that reliably predict the growth of GA over time. The major disadvantage of using GA is that significant, irreversible disease progression has already occurred. The use of drusen volume as a predictor of disease progression and the use of a composite endpoint that incorporates drusen growth, formation of GA, and formation of neovascularization offers an opportunity to study therapies at an earlier stage of AMD with a greater likelihood of preserving better vision over a lifetime.

Conclusions: Anatomic endpoints for the study of nonexudative AMD are needed to accelerate drug development, and the availability of optical coherence tomography algorithms capable of reliably measuring drusen morphology offer the best opportunity to study therapies for iAMD. Ophthalmology 2016;123:1060-1079 © 2016 by the American Academy of Ophthalmology.
Drusen-Associated AMD Progression: Traditional Paradigm

- **Drusen-Only Eyes**
- **Increasing Drusen Volume**
- **Spontaneous Significant Decrease in Drusen Volume (rare)**
- **Exudative Neovascular AMD**
- **Geographic Atrophy**
- **Anti-VEGF Therapy**
Drusen-Associated AMD Progression: Latest Paradigm

Onset of subclinical, non-exudative neovascularization

Drusen-Only Eyes

Increasing Drusen Volume

Spontaneous Significant Decrease in Drusen Volume (rare)

Exudative Neovascular AMD

Anti-VEGF Therapy

Geographic Atrophy
Possible Anatomic Endpoints

Onset of subclinical, non-exudative neovascularization

Drusen-Only Eyes

Increasing Drusen Volume

Spontaneous Significant Decrease in Drusen Volume (rare)

Exudative Neovascular AMD

Anti-VEGF Therapy

Geographic Atrophy
Growth of GA is easily measured and an accepted regulatory endpoint, but would earlier be better?

Growth of Geographic Imaged with Autofluorescence

Area: 5.21 mm²
Volume: 0.899 mm³

Growth and Progression of Drusen Imaged with SD-OCT

RPE Segmentation
### Change in Drusen Volume at 26 Weeks

<table>
<thead>
<tr>
<th>Single-nucleotide polymorphism [at-risk allele]</th>
<th>Drusen genetics (patients)</th>
<th>Change in drusen volume at 26 weeks, mm (SD)</th>
<th>Disease progression and number of alleles, p-value</th>
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</thead>
<tbody>
<tr>
<td>CFH-rs1061170 [C] (Y402H) H1 Haplotype</td>
<td>- - (2)</td>
<td>-0.417</td>
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<tr>
<td></td>
<td>+ - (17)</td>
<td>+0.012 (0.04)</td>
<td>Drusen p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>+ + (11)</td>
<td>+0.025 (0.01)</td>
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</table>

**SNPs investigated (5):** CFH-rs1061170, CFH (rs10490924, HTRA1 (rs10490924, C3 (rs2230199), CFB (rs641153)

**Complete Study**

Drusen Growth Depended on Number of CFH Risk-Alleles Carried by AMD Patients: 52 Weeks (n=30)

<table>
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<th>Change in drusen volume at 52 weeks, mm* (SD)</th>
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<tbody>
<tr>
<td>CFH-rs1061170 [C] (Y402H) H1 Haplotype</td>
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<tr>
<td></td>
<td>+ - (17)</td>
<td>+0.008 (0.061)</td>
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</tr>
<tr>
<td></td>
<td>+ + (11)</td>
<td>+0.026 (0.024)</td>
<td>Drusen p&lt;0.001</td>
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</table>

SNPs investigated (5): CFH-rs1061170, CFH (rs10490924, HTRA1 (rs10490924, C3 (rs2230199), CFB (rs641153)

COMPLETE STUDY
Association of OCT-Derived Drusen Measurements with AMD-Associated Genotypic SNPs in the Amish Population

Venkata Ramana Murthy Chavali 1, Bruno Diniz 2,3, Jiayan Huang 4, Gui-Shuang Ying 4, SriniVas R. Sadda 2,5 and Dwight Stambolian 1,*

1 Department of Ophthalmology, University of Pennsylvania, 313B Stellar-Chance Labs, 422 Curie Blvd., Philadelphia, PA 19104, USA; E-Mail: vchavali@mail.med.upenn.edu
2 Doheny Eye Institute, Los Angeles, CA 90033, USA; E-Mails: bdinizlt@hotmail.com (B.D.); vassadda@gmail.com (S.R.S.)
3 Department of Ophthalmology, Universidade Federal de São Paulo, São Paulo 09920, Brazil
4 Center for Preventive Ophthalmology and Biostatistics, Department of Ophthalmology, University of Pennsylvania, Philadelphia, PA 19104, USA; E-Mails: huangjiayan@gmail.com (J.H.); gsying@mail.med.upenn.edu (G.-S.Y.)
5 Department of Ophthalmology, Keck School of Medicine of the University of Southern California, Los Angeles, CA 90033, USA

* Author to whom correspondence should be addressed; E-Mail: stamboli@mail.med.upenn.edu; Tel.: +1-215-898-0305; Fax: +1-215-573-6728.

Academic Editors: Lindsay Faerrre and Margaret DeAngelis

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Abstract: Purpose: To investigate the association of optical coherence tomography (OCT)-derived drusen measures in Amish age-related macular degeneration (AMD) patients with known loci for macular degeneration.

Methods: Members of the Old Order Amish community in Pennsylvania ages 50 and older were assessed for drusen area, volume and regions of retinal pigment epithelium (RPE) atrophy using a Cirrus High-Definition OCT. Measurements were obtained in the macula region within a central circle (CC) of 3 mm in diameter and a surrounding perifoveal ring (PR) of 3 to 5 mm in diameter using the Cirrus OCT RPE analysis software. Other demographic information, including age, gender and smoking status, were collected. Study subjects were further genotyped to determine their risk for the AMD-associated SNPs in the SYN3, LIPC, ARMS2, SYN3, LIPC, CETP, CFI and CFH genes using TaqMan genotyping assays. The association of genotypes with OCT measures were assessed using linear trend p-values calculated from univariate and multivariate analyses of 216 subjects and 432 eyes.

Genotypic associations between OCT drusen area and volume in the Amish
Univariate and multivariate analyses of 216 subjects and 432 eyes
SNPs investigated (8): CFH (rs12038333), C3, CFI, CFB, ARMS2, SYN3, LIPC, CETP
Number of CFH risk alleles associated with drusen area and drusen volume (p= 0.04) after adjustment for multiple comparisons
If growth of GA can be slowed, then imagine the impact on AMD if drusen growth can be slowed?

Growth of Geographic Imaged with Autofluorescence

Area: 5.21 mm²
Volume: 0.899 mm³

RPE Segmentation

Growth and Progression of Drusen Imaged with SD-OCT
Complement Inhibition for AMD: What’s the best complement target?

- Best clinical trial endpoint?
- Best complement target?
- Best dose?
- Best dosing interval?
- Best route for drug delivery?
AMD Clinical Trials with Complement Inhibitors

- Anti-Factor D Fab (intravitreal)
  - Lampalizumab: Genentech/Roche

- Anti-C5 drugs
  - Anti-C5 monoclonal antibodies:
    - LFG316±Anti- Properdin: Novartis (intravitreal)
    - Eculizumab: Alexion (intravenous)
  - Anti-C5 aptamer (Zimura): Ophthotech (intravitreal)

- Prevent membrane attack complex
  - AAV gene therapy delivers sCD59 (HMR59): Hemera (intravitreal)

- Anti-C3 cyclic peptide (intravitreal)
  - POT-4: Potentia, APL-2: Apellis
AMD Clinical Trials with Complement Inhibitors

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  - POT-4: Potentia, APL-2: Apellis
The Complement Pathway and Factor D Inhibition

- Lectin Pathway
- Classical Pathway
- Alternative Pathway

C3 → C3a (Inflammation) → C3b → C5 (Inflammation) → C5a → C5b (MAC) → Cell death, secretion, lysis, or proliferation

C5b → Cell removal, Antigen uptake by APCs

Most of the complement pathway remains intact
AMD Clinical Trials with Complement Inhibitors

- Anti-Factor D Fab (intravitreal)
  - Lampalizumab: Genentech/Roche

- Anti-C5 drugs
  - Anti-C5 monoclonal antibodies:
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- Anti-C3 cyclic peptide (intravitreal)
  - POT-4: Potentia, APL-2: Apellis
The Complement Pathway and C5 Inhibition

C3, C3a, and C3b are unaffected

Cell removal, Antigen uptake by APCs

Cell death, secretion, lysis, or proliferation

Inflammation

C3a

C3b

Inflammation

C5a

C5b

STOP

MAC
AMD Clinical Trials with Complement Inhibitors

- Anti-Factor D Fab (intravitreal)
  - Lampalizumab: Genentech/Roche
- Anti-C5 drugs
  - Anti-C5 monoclonal antibodies:
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### The Complement Pathway and C5 Inhibition

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<thead>
<tr>
<th>Pathway</th>
<th>Components</th>
<th>Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lectin Pathway</td>
<td>C3, C3a, C3b, C5, C5a</td>
<td>Inflammation, Cell death, secretion, lysis, or proliferation</td>
</tr>
<tr>
<td>Classical Pathway</td>
<td>C3, C3a, C3b, C5, C5a</td>
<td>Inflammation, Cell removal, Antigen uptake by APCs</td>
</tr>
<tr>
<td>Alternative Pathway</td>
<td>C3, C3a, C3b, C5, C5a, C5b</td>
<td>Inflammation, Cell death, secretion, lysis, or proliferation</td>
</tr>
</tbody>
</table>

C3, C3a, C3b, C5, C5a, and C5b are unaffected.
AMD Clinical Trials with Complement Inhibitors

- Anti-Factor D Fab (intravitreal)
  - Lampalizumab: Genentech/Roche

- Anti-C5 drugs
  - Anti-C5 monoclonal antibodies:
    - LFG316± Anti-Properdin: Novartis (intravitreal)
    - Eculizumab: Alexion (intravenous)
  - Anti-C5 aptamer (Zimura): Ophthotech (intravitreal)

- Prevent membrane attack complex
  - AAV gene therapy delivers sCD59 (HMR59): Hemera (intravitreal)

- Anti-C3 cyclic peptide (intravitreal)
  - POT-4: Potentia, APL-2: Apellis
• Anti-C3 cyclic peptide (13 amino acids)
• Given as intravitreal injection
• When injected at a dose of 1.05 mg, drug spontaneously formed a deposit that slowly decreased over months
• Drug needed to be reformulated
• Anti-C3 cyclic peptide (13 amino acids)
• Given as intravitreal injection
• When injected at a dose of 1.05 mg, drug spontaneously formed a deposit that slowly decreased over months
• Drug needed to be reformulated
Reformulated POT-4 = APL-2

Cyclic peptide (POT-4): 13 amino acids

Polyethyleneglycol (PEG)

Cyclic peptide (POT-4): 13 amino acids

Peptides of the APL-2 family bind to a pocket of C3 and inhibit activation*


Subcutaneous or intravitreal injections
The Complement Pathway and APL-2

- Complete Inhibition of the Complement Pathway

**Lectin Pathway**
- Cell death, secretion, lysis, or proliferation

**Classical Pathway**
- Inflammation
  - C3a
  - C3b
  - C5a
  - C5b
  - MAC
  - Cell death, secretion, lysis, or proliferation

**Alternative Pathway**
- Cell removal, Antigen uptake by APCs

**APL-2**

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FILLY Phase 2 Results and Phase 3 Study Design

Frank Holz, MD,
Chairman and Professor,
Department of Ophthalmology,
University of Bonn, Germany
Phase 2 Study Design

Eligible Patients with Geographic Atrophy*
246 subjects in 43 sites†

Single Masked
Randomized 2:2:1:1

APL-2 15 mg
Monthly
(AM) N=86

APL-2 15 mg
Every Other Month
(AEOM) N=79

Sham
Monthly
(SM) N=41

Sham
Every Other Month
(SEOM) N=40

Randomization

Treatment Period‡

Follow up

AM (n=86)
AEOM (n=79)
SM (n=41)
SEOM (n=40)

D0 M1 M2 M3 M4 M5 M6 M7 M8 M9 M10 M11 M12
D0 M2 M4 M6 M8 M10 M12
D0 M1 M2 M3 M4 M5 M6 M7 M8 M9 M10 M11 M12
D0 M2 M4 M6 M8 M10 M12

M15 M18
M15 M18
M15 M18
M15 M18

*Confirmed by the central reading center using FAF images, †Not counting the 3 satellite sites. ‡Subjects also had a safety visit at Day 7
**Endpoints**

**Primary efficacy endpoint**
Change in square root geographic atrophy (GA) lesion size from baseline to month 12.

**Primary safety endpoint**
Number and severity of local and systemic treatment emergent adverse events (TEAEs).
Key Inclusion/Exclusion Criteria

- **Inclusion Criteria:**
  - Age ≥ 50 years
  - GA due to AMD confirmed by the central reading center using FAF images:
    - Total GA area 2.5 to 17.5 mm$^2$ (1 to 7 DA) at Screening
    - For multifocal GA, at least one lesion with ≥ 1.25 mm$^2$ (0.5 DA)
    - Can be measured separately from any area of peripapillary atrophy
    - Perilesional hyperautofluorescence present (any pattern)
  - BCVA (ETDRS charts) of 24 letters or better (20/320 Snellen equivalent)

- **Exclusion Criteria:**
  - GA due to causes other than AMD, or retina disease other than AMD
  - History or current evidence of neovascular AMD

  **Note:** No exclusion criteria associated with the fellow eye
## Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Sham Injections n=81</th>
<th>APL-2 EOM n=79</th>
<th>APL-2 Monthly n=86</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bilateral GA, n (%)</strong></td>
<td>72 (90.0%)</td>
<td>64 (82.1%)</td>
<td>71 (85.5%)</td>
</tr>
<tr>
<td><strong>History of CNV in Fellow Eye, n (%)</strong></td>
<td>29 (35.8%)</td>
<td>28 (35.4%)</td>
<td>36 (41.9%)</td>
</tr>
<tr>
<td><strong>GA lesion size, mean, mm² (SD)</strong></td>
<td>8.2 (4.1)</td>
<td>8.9 (4.5)</td>
<td>8.0 (3.8)</td>
</tr>
<tr>
<td><strong>BCVA score, mean letters (SD)</strong></td>
<td>59.8 (17.2)</td>
<td>58.4 (16.0)</td>
<td>59.8 (15.7)</td>
</tr>
<tr>
<td><strong>BCVA score (Snellen equivalent)</strong></td>
<td>20/63</td>
<td>20/80</td>
<td>20/63</td>
</tr>
<tr>
<td><strong>LL-BCVA score, mean letters (SD)</strong></td>
<td>33.6 (17.8)</td>
<td>31.4 (17.1)</td>
<td>36.3 (16.6)</td>
</tr>
</tbody>
</table>
APL-2 Slows GA Growth at 12 Months (square root)

Modified Intent to Treat population (mITT), Observed, Mixed-Effect Model

Sham Injections
APL-2 EOM
APL-2 Monthly

Change from baseline in square root GA lesion growth (mm)

20% lesion growth difference p=0.067 vs Sham

29% lesion growth difference p=0.008 vs Sham
## Sensitivity Analysis

<table>
<thead>
<tr>
<th>Population</th>
<th>Sham Pooled</th>
<th>APL-2 EOM</th>
<th>APL-2 Monthly</th>
</tr>
</thead>
<tbody>
<tr>
<td>mITT Population (primary endpoint)</td>
<td>n*</td>
<td>80</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>LS Mean (SE)</td>
<td>0.35 (0.025)</td>
<td>0.28 (0.026)</td>
</tr>
<tr>
<td></td>
<td>Reduction vs Sham</td>
<td>20%</td>
<td>29%</td>
</tr>
<tr>
<td></td>
<td>p-value (vs Sham)</td>
<td>0.067</td>
<td>0.008</td>
</tr>
<tr>
<td>Per protocol Population</td>
<td>n*</td>
<td>73</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>LS Mean (SE)</td>
<td>0.35 (0.026)</td>
<td>0.28 (0.027)</td>
</tr>
<tr>
<td></td>
<td>Reduction vs Sham</td>
<td>20%</td>
<td>26%</td>
</tr>
<tr>
<td></td>
<td>p-value (vs Sham)</td>
<td>0.05</td>
<td>0.019</td>
</tr>
</tbody>
</table>

* Number of subjects who contributed to the analysis
Lesion Growth by Six-month Periods *(square root)* – 12 months

![Graph showing lesion growth by six-month periods for Sham Injections, APL-2 EOM, and APL-2 Monthly. The graph indicates that APL-2 EOM and APL-2 Monthly show a significant difference in lesion growth compared to Sham, with APL-2 Monthly showing the most significant difference.](image_url)

33% lesion growth difference vs sham p=0.01

47% lesion growth difference vs sham p < 0.001
FILLY Sham Group Behaved Consistently with Recent Publication

<table>
<thead>
<tr>
<th>Measure</th>
<th>Sham Pooled (n=598)</th>
<th>Lampalizumab, 10 mg q4w (n=596)</th>
<th>Lampalizumab, 10 mg q6w (n=603)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change from baseline in square root GA lesion growth (mm) at 48 wk, mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted mean (SE)</td>
<td>0.342 (0.007)</td>
<td>0.349 (0.007)</td>
<td>0.352 (0.007)</td>
</tr>
<tr>
<td>Difference in means (vs sham pooled)</td>
<td>0.006</td>
<td>0.010</td>
<td></td>
</tr>
</tbody>
</table>

Holz, F.G., et al., Efficacy and Safety of Lampalizumab for Geographic Atrophy Due to Age-Related Macular Degeneration: Chroma and Spectri Phase 3 Randomized Clinical Trials. JAMA Ophthalmol, 2018
After cessation of treatment at 12 months, GA growth resumes but treatment effect is maintained through 18 months (square root).

**Modified Intent to Treat population (mITT), Observed, Mixed-Effect Model**

- **16% lesion growth difference**
  - p = 0.097 vs Sham

- **20% lesion growth difference**
  - p = 0.044 vs Sham

**Graph Details**

- **Y-axis**: Change from baseline in square root GA lesion growth (mm)
- **X-axis**: Time (2 months, 6 months, 12 months, 18 months)
- **Legend**:
  - Sham Injections
  - APL-2 EOM
  - APL-2 Monthly

**Graph Notes**

- **Change from Baseline**
  - Sham Injections: 0.49
  - APL-2 EOM: 0.41
  - APL-2 Monthly: 0.39
Lesion Growth by Six-month Periods (square root) – 18 Months

Sham Injections

APL-2 EOM

APL-2 Monthly

Data from subjects with a measurable GA lesion size at Months 6 & 12 & 18
GA Growth Comparison: Fellow Eye vs Study Eye

*post hoc analysis*

Includes patients from the Bilateral GA Population
Best-corrected Visual Acuity

No differences were observed in visual outcomes between groups.

Modified Intent to Treat population (mITT), Observed, Mixed-Effect Model
A mixed effect model with main effects of treatment, visit and GA lesion at baseline, and interactions of treatment × visit, visit × baseline.
mITT = All subjects receiving at least one injection and having at least one FAF image after day 1
## Adverse Event Profile

<table>
<thead>
<tr>
<th>Adverse Event n (%) of subjects with events</th>
<th>APL-2 Monthly N=86</th>
<th>APL-2 Every Other Month N=79</th>
<th>Sham Pooled N=81</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular SAEs in study eye*</td>
<td>4 (4.7%)</td>
<td>2 (2.5%)</td>
<td>1 (1.2%)</td>
</tr>
<tr>
<td>Systemic (non-ocular) SAEs</td>
<td>19 (22.1%)</td>
<td>24 (30.4%)</td>
<td>23 (28.4%)</td>
</tr>
<tr>
<td>Treatment related ocular AEs in the study eye</td>
<td>22 (25.6%)</td>
<td>11 (13.9%)</td>
<td>0</td>
</tr>
<tr>
<td>Treatment related systemic (non-ocular) AEs</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ocular SAEs</th>
<th>APL-2 Monthly N=86</th>
<th>APL-2 EOM N=79</th>
<th>Sham Pooled N=81</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endophthalmitis*</td>
<td>2 (2.3%)</td>
<td>1 (1.3%)</td>
<td>0</td>
</tr>
<tr>
<td>IOP increased</td>
<td>1 (1.2%)†</td>
<td>1 (1.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>1 (1.2%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>0</td>
<td>0</td>
<td>1 (1.2%)</td>
</tr>
</tbody>
</table>

*2 culture positive for coagulase-negative Staphylococcus. 1 culture negative in the monthly group. †2 events in a subject
New onset exudation – 18 months

<table>
<thead>
<tr>
<th></th>
<th>APL-2 Monthly</th>
<th>APL-2 EOM</th>
<th>Sham Pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Subjects</td>
<td>n = 86</td>
<td>n = 79</td>
<td>n = 81</td>
</tr>
<tr>
<td>Subjects with wAMD in Study eye (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With History of CNV in Fellow Eye</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No CNV History in Fellow Eye</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>n = 36</th>
<th>n = 28</th>
<th>n = 29</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with wAMD in Study eye (%)</td>
<td>n = 50</td>
<td>n = 51</td>
<td>n = 52</td>
</tr>
<tr>
<td>Subjects with wAMD in Study eye (%)</td>
<td></td>
<td>n = 51</td>
<td>n = 52</td>
</tr>
<tr>
<td>Subjects with wAMD in Study eye (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Majority of patients that developed exudation had minor loss of vision and were treated with anti-VEGF therapy (avastin, ranibizumab or aflibercept)
- 6 patients developed wet AMD in the 12-18 month non-treatment period (5/6 had fellow eye wet AMD)
Phase 3, Multi-Center, Randomized, Double-Masked, Sham-Controlled Study to Compare the Efficacy and Safety of APL-2 in GA Secondary to AMD
# Phase 3 Study Overview

## 2 Global Studies

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients with Geographic Atrophy secondary to AMD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1° Endpoint</strong></td>
<td>Change in total area of GA lesion(s) based on FAF at Month 12</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Double Masked, Randomized 2:1:2:1</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>15 mg/0.1 mL Intravitreal Injection vs. Sham Injection</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>600 Subjects from approx. 100 multinational sites per study</td>
</tr>
</tbody>
</table>

Each study will have the following design:

- **Screening - R:2:1:2:1**
- **2 years**
- APL-2 Monthly N = 200
- APL-2 EOM N = 200
- Sham Monthly N = 100
- Sham EOM N = 100
Study Population

No changes in Inclusion/Exclusion criteria from Filly Phase 2

• Key inclusion criteria - Study eye:
  – BCVA > 24 letters by ETDRS (20/320 Snellen equivalent)
  – The GA lesion must:
    ▪ Total GA: ≥ 2.5 and ≤ 17.5 mm²
    ▪ If GA is multifocal, at least one focal lesion must be ≥ 1.25 mm² (0.5 DA)
    ▪ Presence of any pattern of perilesional hyperautofluorescence

• Neovascular AMD in fellow eye is not exclusionary
Key Endpoints

• Primary:
  - Change from baseline to Month 12 in total area of GA lesion(s) in the study eye (in mm$^2$) based on Fundus Autoflourescence (FAF)

• Secondary:
  - Best-corrected visual acuity (BCVA), low luminance BCVA, low luminance deficit in the study eye
  - Reading speed (study eye), as assessed by Minnesota Reading or Radner Reading (MNRead) Charts (in select sites)
  - Microperimetry using MAIA device
  - National Eye Institute Visual Functioning Questionnaire 25-Item Version (NEI VFQ-25) distance activity subscale score
  - Functional Reading Independence Index (FRI) composite score in the study eye
• APL-2 reduced the progression of GA secondary to AMD in the Phase 2 GA trial (n=246)

• Results correlated to treatment frequency with increasing effect size over time

• Further evidence from intra-patient control

• Upon discontinuation of APL-2, treatment effect declined

• Global Phase 3 study initiated
Panel Discussion

Jason S. Slakter, MD
Clinical Professor of Ophthalmology, NYU School of Medicine
Director Digital Angiography Reading Center