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# A Clinical and Preclinical Assessment of Clinical Trials for Dry Age-Related Macular Degeneration

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Age-related macular degeneration (AMD) is the leading cause of blindness for the elderly in high-income countries. Although multivitamin antioxidant nutrients can slow the progression of intermediate "dry" or non-neovascular AMD, no treatment can halt or reverse any stage of dry disease. Multiple biologic pathways have been implicated in AMD pathobiology, including the complement pathway. These pathways have been targeted by various approaches in clinical trials. To date, no treatment has reached their prespecified primary end point in 2 phase III trials, a requirement by the US Food and Drug Administration for a new drug approval. Here, we describe perspectives on the failures and possible successes of various clinical trials that will guide further investigation. These perspectives will also discuss clinical trial design issues to consider in future investigations, and how recent insights into AMD pathobiology might both provide additional explanation for trials not reaching the prespecified primary end points and offer direction for identifying prioritized treatment targets. *Ophthalmology Science 2022;2:100213* © *2022 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Age-related macular degeneration (AMD) is the leading cause of visual impairment among the elderly in western societies. Worldwide, the number of individuals with AMD is projected to increase from 196 million in 2020 to 288 million by 2040.[1] In the United States, around 11 million people have AMD, and monitoring and treatment for this disease costs ∼ $30 billion each year.[2,3] These numbers are expected to rise as the population ages. Although anti-VEGF treatment has revolutionized treatment for the neovascular form of AMD and antioxidant micronutrients can slow the progression of intermediate-stage disease, currently, no treatment or prevention is available for patients who suffer from either early- or late-stage dry AMD.[4] As a result, preclinical and clinical researchers have devoted tremendous resources to understanding dry AMD pathogenesis on which to develop therapy for both early and late-stage dry disease. Some of these targets have matured sufficiently to be tested in clinical trials. Here, the status of clinical trials for dry AMD that have provided insight into our understanding of dry AMD will be described, as well as the clinical and preclinical barriers that must be overcome to fully optimize treatment for dry AMD.

## Rational for Geographic Atrophy as a Target of Clinical Trials on Dry AMD

For any drug to be approved by the US Food and Drug Administration (FDA), a primary prespecified end point approved by the FDA, must be demonstrated in 2 large randomized prospective clinical trials. For most ophthalmic clinical trials, visual acuity (VA) has been the standard primary end point. In early AMD, VA remains intact and does not correlate with disease severity. For example, drusen accumulation, a hallmark AMD lesion, or other classic structural features of AMD do not correlate with VA.[5] Furthermore, drusen can resolve without apparent functional effects.[6] In addition, VA loss occurs slowly and typically manifests only in the later course of late-stage dry AMD. As such, VA is an unsuitable primary end point for clinical trials on dry AMD. Currently, no functional assessment of vision has been validated to serve as a primary end point for a clinical trial on dry AMD. Surrogate end points or anatomic biomarkers can be used as a primary end point if they reflect visual function or predict future vision loss. In geographic atrophy (GA), the late stage of dry



https://doi.org/10.1016/j.xops.2022.100213
ISSN 2666-9145/22

AMD, atrophy of the photoreceptors, retinal pigment epithelium (RPE), and choriocapillaris typically develops in the parafovea and when it enlarges to involve the fovea, major vision loss ensues. Logically, preventing GA expansion to involve the fovea would preserve central vision. Geographic atrophy area can be accurately measured, and its growth can be reliably predicted.[7] As a result, the FDA has allowed slowing of GA enlargement as a suitable, surrogate primary end point for clinical trials in GA.[8] Geographic atrophy is often measured using fundus photography and autofluorescence as well as other modalities, such as OCT, to analyze the lesion surface area and perimeter quantifications, alongside other measurements such as number of lesions and atrophy location. Different clinical trials may focus on different GA measurements. Of the various end points, perimeter and area growth rate have been shown to be associated.[9] Square root analyses are also often used to examine the reproducibility of results; however, studies have shown that square root transformation of GA measurements diminishes the correlation between the baseline measurements and growth rate.[10] This factor should be considered when designing the clinical trials and patient exclusion criteria.

## Lessons Learned from Selected Clinical Trials

The pathogenesis of AMD is complex and incompletely understood. From epidemiologic, histopathologic, genetic, epigenetic, and preclinical investigation, several dysregulated biologic processes have emerged as substantial contributors to disease development and progression. Thus far, genetic variants associated with substantial AMD risk have been identified that involve innate immunity, extracellular matrix regulation, and lipid metabolism.[11] For example, genetic variations in complement pathway genes, including complement factor H, have placed emphasis on innate immune dysregulation in AMD pathobiology.[12–15] Likewise, the strong link of the *Age-Related Maculopathy Susceptibility 2/HtrA Serine Peptidase 1* (*HTRA1*) polymorphism with AMD risk has implicated alterations with extracellular matrix or Bruch membrane with AMD disease development.[16,17] Cigarette smoking is the strongest environmental risk factor associated with AMD risk.[18–22] Given the ~ 5000 toxins and ~ $10^{14}$ oxygen free radicals in 1 puff of smoke, oxidative stress and failure of cellular antioxidant protective systems have been a focus of intensive study.[23,24] Because mitochondria produce the majority of cellular oxygen free radicals during oxidative phosphorylation, it is not surprising that mitochondrial impairment has emerged as a pathogenic factor in AMD.[25–28] As a result, these pathways, specifically those involved with complement dysregulation and *Age-Related Maculopathy Susceptibility 2/HTRA1* have been the focus of drug development for dry AMD treatment and have matured to the point that they are being tested in clinical trials. According to Clinicaltrials.gov, at the time of the writing of this manuscript, 1871 clinical trials have been conducted on AMD, of which 102 studies have focused on GA. To date, no drug has been approved by the FDA for treating GA.

Table 1 summarizes the results of the clinical trials that are discussed in this perspective. Several trials have focused on potentially normalizing complement function

Table 1. Summary of Clinical Trials

| Phase | Trial Name | Drug | Target | Frequency | Route | Tx Duration | Sample Size | Results |
|---|---|---|---|---|---|---|---|---|
| II | | Pegcetacoplan | C3 | 4 wks | IVT | 12 mos | 127 | 29% GA growth decrease 29%; $P = 0.008$ |
| | | | | 8 wks | IVT | 12 mos | 119 | 20% GA growth decrease; $P = 0.067$ |
| III | OAKS | Pegcetacoplan | C3 | 4 wks | IVT | 12 mos | 637 | 22% GA growth decrease; $P = 0.0003$ |
| | | | | 8 wks | IVT | 12 mos | | 16% GA growth decrease; $P = 0.0052$ |
| III | DERBY | Pegcetacoplan | C3 | 4 wks | IVT | 12 mos | 621 | 12% GA growth decrease; $P = 0.0528$ |
| | | | | 8 wks | IVT | 12 mos | | 11% GA growth decrease; $P = 0.0750$ |
| II | FILLY | Avacincaptad | C5 | 4 wks | IVT | 12 mos | 177 | 27% GA growth decrease; $P = 0.0072$ |
| | | | | 4 wks | IVT | 12 mos | 167 | 28% GA growth decrease; $P = 0.0051$ |
| II | MAHALO | Lampalizumab | FD | 4 wks | IVT | 18 mos | 82 | 20% GA growth decrease; $P = 0.12$ |
| | | | | 8 wks | IVT | 18 mos | 81 | −7.7% GA growth decrease; $P = 0.55$ |
| III | CHROMA | Lampalizumab | FD | 4 wks | IVT | 18 mos | 452 | GA area growth decrease −0.02 $mm^2$; $P = 0.80$ |
| | | | | 6 wks | IVT | 18 mos | 455 | GA area growth decrease 0.16 $mm^2$; $P = 0.048$ favor sham |
| III | SPECTRI | Lampalizumab | FD | 4 wks | IVT | 18 mos | 491 | GA area growth decrease 0.05 $mm^2$; $P = 0.59$ |
| | | | | 6 wks | IVT | 18 mos | 484 | GA area growth decrease 0.09 $mm^2$; $P = 0.27$ |
| II | | Eculizumab | C5 | 2 wks | IVT | 6 mos | 20 | GA area not reduced |
| II | GATHER | Tesidolumab | C5 | 4 wks | IVT | 12 mos | 50 | GA area not reduced |
| I | ReCLAIM1 | Elamiprimide | CL | Daily | SQ | 24 wks | 19 | No serious AEs |
| II | ReCLAIM2 | Elamiprimide | CL | Daily | SQ | 48 wks | 176 | No change in LLVA and GA area not reduced |
| I | | Anti-*HTRA1* | *HTRA1* | 4 wks | IVT | 12 wks | 28 | No serious AEs |

AE = adverse event; C3 = complement C3; C5 = complement C5; CL = cardiolipin; FD = complement factor D; GA = geographic atrophy; *HTRA1* = *HtrA serine peptidase 1*; LLVA = low luminance visual acuity; IVT = intravitreal; SQ = subcutaneous; Tx = treatment.

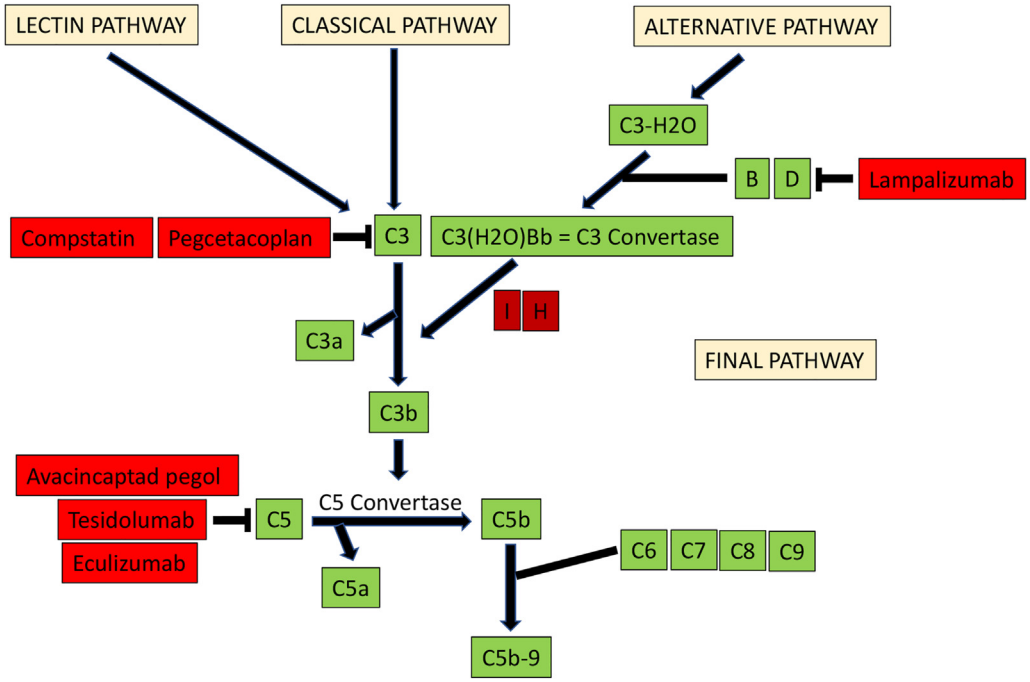


**Figure 1.** Diagram of the complement pathway. The specific complement target of drugs that have reached clinical trial and are discussed in this perspective are highlighted.

(Fig 1). Because of the strong link of complement factor H polymorphisms with AMD risk, the alternative complement pathway has been the focus of multiple clinical trials. Complement factor D is the rate-limiting enzyme in the alternative complement pathway. Lampalizumab is an antigen-binding fragment (Fab) of a humanized monoclonal antibody against complement factor D. In a phase II clinical trial,[29] lampalizumab was delivered intravitreally each month or every other month for 18 months. In the study group ($n = 42$), GA growth was reduced by 20% ($P = 0.12$) versus a sham treatment. Interestingly, GA growth was reduced by 44% in individuals who carried the complement factor I risk allele. These results prompted 2 phase III trials, Chroma and SPECTRI, which comprised, at that time, the largest studies of GA. In the Chroma trial, patients were given intravitreal lampalizumab every month, whereas in the SPECTRI trial, patients received intravitreal lampalizumab every 6 weeks for 96 weeks. A total of 906 patients participated. Each trial showed that lampalizumab did not reduce GA enlargement compared with sham treatment across 48 weeks.[30]

Complement factor C3 is activated by all 3 complement pathways and is upstream of its major effectors including C3a, C5a, and the membrane attack complex. Compstatin and related analogs such as APL-1 are peptides that specifically bind C3 and prevent its activation.[31,32] Pegcetacoplan, a pegylated form of APL-1, was tested in a GA phase II trial via intravitreal delivery monthly or every other month for 12 months and the GA area was assessed at 15 and 18 months. With a sample size of 240 patients, GA enlargement, measured through the mean change in square root of lesion size, was reduced by 29% ($P = 0.008$) with monthly injections and 20% ($P = 0.067$) with every other month injections compared with sham treatment. The effect was greater after 12 months of treatment. Geographic atrophy growth was reduced by 45% ($P = 0.0004$) with monthly treatment and 33% ($P = 0.009$) with every other month injections relative to sham treatment. Interestingly, the treatment effect declined after stopping treatment. Pegcetacoplan treatment did not influence the GA growth rate in patients with complement factor H, complement factor I, complement factor C2/complement factor B, and C3 genetic variants.[33]

These favorable results prompted 2 phase III double-masked clinical trials, DERBY and OAKS, testing pegcetacoplan in GA. The 12-month results were presented at the 2021 Retina Society meeting. In the OAKS and DERBY trials, 638 and 621 patients, respectively, were enrolled. In both trials, patients with GA received monthly or every other month intravitreal injections of pegcetacoplan or sham treatment for 12 months. Although OAKS met the primary end point of a 22% ($P = 0.0003$) decrease with monthly and a 16% ($P = 0.0052$) decrease in GA growth with every other month treatment at 12 months relative to sham treatment, respectively, DERBY did not reach its primary end point. In the DERBY trial, patients who received monthly treatment had a 12% reduction in GA growth ($P = 0.0528$) and those who received every other month treatment had an 11% ($P = 0.0750$) reduction in GA growth at 12 months. With a combined analysis across both trials, GA growth was reduced by 17% ($P < 0.0001$) with monthly and 14% ($P = 0.0012$) with every other month treatment at 12 months. In a press release of March 16, 2022, Apellis presented 18-month follow-up data for DERBY and OAKS.

Pegcetacoplan treatment showed further reduction in lesion growth from baseline to month 18 (all nominal $P$ values $<$ 0.05). In DERBY, monthly pegcetacoplan reduced GA enlargement by 13% ($P = 0.0254$) and every other month treatment reduced GA enlargement by 12% ($P = 0.0332$) relative to sham-treated patients. In OAKS, monthly pegcetacoplan reduced GA enlargement by 22% ($P < 0.0001$) and every other month treatment reduced GA enlargement by 16% ($P = 0.0018$) relative to sham-treated patients.

In a highly controversial decision made in June 2021, the FDA approved aducanumab-avwa as a treatment for Alzheimer's disease using the accelerated approval pathway that was based on the monoclonal antibody's ability to lower β-amyloid levels.[34] In March 2019, Biogen discontinued their 2 phase III clinical trials, ENGAGE and EMERGE, because their analysis indicated that neither trial was likely to reach their primary end point of slowing cognitive impairment using changes in the Clinical Dementia Rating-Sum of Boxes score.[34] In October, 2019, Biogen then announced that they were going to seek FDA approval based on their additional analyses of a larger dataset that was eventually published in March, 2022.[35] These subsequent efficacy analyses included a larger data set collected up to futility declaration and followed the prespecified statistical analyses. The primary end point was met in EMERGE, but not in ENGAGE. In contrast to their usual policy of requiring 2 phase III clinical trials to achieve their specified primary end points, the FDA approved aducanumab. Because DERBY did not reach the primary end point of reducing GA growth at 12 months, but did so after 18 months, it will be interesting to learn whether the FDA approves pegcetacoplan, especially given their recent decision to approve aducanumab and the resultant controversy associated with this decision.

Complement C5, downstream of C3 in the terminal pathway, forms the anaphylatoxin C5a when cleaved, which activates proinflammatory cytokines, and C5b, which initiates membrane attack complex formation. Avacincaptad pegol (Zimura), a pegylated RNA aptamer that inhibits C5, was tested in a phase II GA trial. This study, comprised of 286 patients, used a stratified randomization protocol by the location and size of the GA lesions, as well as the pattern of fundus autofluorescence at the junctional zone of GA. Avacincaptad pegol was administered intravitreally every month for 12 months. Patients who received avacincaptad pegol had a 28% reduction in GA growth at 12 months ($P = 0.0072$) as compared with sham-treated patients. Because of the randomized stratification protocol used, and the lack of adverse effects, avacincaptad pegol proceeded to phase III trials, "GATHER2," which are ongoing.[36]

Two different phase II clinical trials also focused on inhibiting C5, through tesidolumab and eculizumab. With a sample size of 50 patients, tesidolumab (LFG316), a humanized monoclonal antibody against C5, when administered intravitreally every month, did not reduce GA growth after 12 months (NCT01527500, clinicaltrials.gov). Eculizumab, which is approved for treatment of paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremia, was administered IV for 24 weeks (sample size of 20 patients). At 26 weeks, and then 3 and 6 months later, despite reaching therapeutic blood levels that inhibited C5 activity to $<$ 1% by week 2, eculizumab did not decrease GA growth.[37]

Although 14 different complement inhibitors have been explored through almost 40 clinical trials to date, the aforementioned studies represent the most recent directions and results of targeting the complement pathway. Cumulatively, these trials have mixed outcomes. What have we learned? First, compared with the phase II lampalizumab, eculizumab, and tesidolumab trials, the C3 inhibitor (pegcetacoplan) and C5 inhibitor (Zimura) trials were better powered to provide insights for deciding whether or not to proceed to phase III clinical trials. In the GATHER1 Zimura trial, a randomization scheme that took into account the GA size, location, and fundus autofluorescent pattern of the GA's transition zone between treatment and sham groups was used. As reported in the phase III pegcetacoplan trial, pegcetacoplan had a greater effect in patients with extrafoveal lesions at baseline (https://investors.apellis.com/static-files/fe6d8c27-e1b2-4c87-b77f-aa5cb249bacf).[38] Given that the GA phenotype varies from patient to patient, balancing these phenotypic differences may help to elucidate which patients might benefit from treatment.

Several factors potentially contributed to the unfavorable results in the phase III lampalizumab trial. For example, an unusually low level of statistical significance ($P = 0.12$) for reduction in GA growth was allowed in the decision to advance to a phase III trial. Although patients with the factor I polymorphism had a more substantial reduction in GA growth, the prevalence of this single nucleotide polymorphism is in the cohort studied was small. As a result, the low enrollment of patients with this genetic variant did not influence lampalizumab's potential treatment benefit of either this subpopulation or the overall cohort in the phase III trials. Although monthly and every other month lampalizumab treatment was not beneficial, monthly and every 6-week treatment was instituted in the phase III trial. It is unclear if the dose of intravitreal lamplizumab was sufficient to reach therapeutic levels in the RPE/Bruch membrane, where complement overactivity is thought to be pathogenic, although a phase II study of every 2-week injection of lampalizumab also did not show any efficacy (https://clinicaltrials.gov/ct2/show/NCT02288559).[39] Likewise, in the phase II eculizumab trial, it is possible that IV administration failed to provide therapeutic intraocular inhibitory levels despite C5 activity inhibition in the blood. Furthermore, the study duration of 26 weeks, which was substantially shorter than the other trials, potentially prevented identifying any treatment benefit, especially given the slow growth rate of GA lesions. Finally, both anti-C5 eculizumab and tesidolumab have molecular weights of 150 kDa, whereas avacincaptad pegol is 50 kDa. It is possible that either the reduced tissue distribution or the relative moles delivered relative to avacincaptad pegol because of the size differences were insufficient to see a treatment effect. Finally, it is critical to understand that serum and potentially disease levels of C5 and C3 are quite high in the range of 75 ug/ml and 1000 ug/ml, respectively. Thus, future trials testing new therapeutics for GA growth reduction should consider the study's power, a sufficient study duration, the route of administration and

its pharmacokinetics to the specific target tissue, the therapeutic concentration needed to achieve complement level reduction and a balanced randomization scheme that considers size, location, and fundus autofluorescent pattern of the GA.

Although expansion of GA lesion area is a validated "surrogate" end point for advanced dry AMD clinical trials, currently a reliable and practical functional end point is unknown. In addition, a surrogate or functional end point for early and intermediate AMD has not been elucidated despite intensive investigation. The parafoveal macula undergoes the earliest changes in AMD and GA; specifically, the rod dominant parafovea undergoes the earliest changes, including rod outer segment shortening and then rod cell death that is coincident with RPE abnormalities.[40] Recently, Zekavat et al[41] showed that photoreceptor segment thinning, as seen on OCT, is an early biomarker for AMD and can precede RPE-Bruch membrane complex thickening by decades. The current functional vision tests being investigated test much of this region and include dark adaptometry, microperimetry, quantitative contrast sensitivity (CSF), and low luminance VA (LLVA).[42–45] Although VA can be unaffected, parafoveal injury affects rods and hence, patients may experience difficulty adapting to dark environments without changes in central VA. Specifically, dark adaptometry can be used as a metric when VA is stable in AMD. The rod intercept time, which represents delayed dark adaptation, correlates with AMD severity.[46] However, at present, the protocols are not standardized, dark adaptation changes develop slowly over years, and results can be influenced by cataract severity and intraocular lens implants.

Microperimetry is a measure of macular retinal sensitivity in which accurate threshold light sensitivity is measured at specific macular locations. When tested under photopic light conditions, cones are primarily tested, whereas under scotopic or mesopic conditions, rods can be queried.[47] Microperimetry is reliable and repeatable; however, its use is limited by its expense, tedious and lengthy testing, and reliance on the expertise of the examiner.

Low luminance visual acuity is a potential alternative to test the functional changes in AMD. Low luminance visual acuity uses a standard VA chart. The patient's vision is tested under normal lighting conditions and in low-light conditions, often by adding a neutral density filter in front of the test eye. The assay is simple and rapid, which is an advantage in any clinical trial. Low luminance visual acuity has been previously used in eyes with nonfoveal GA to show that low luminance deficit, or the difference between LLVA and best-corrected VA, predicts subsequent vision loss and GA enlargement.[48] Low luminance visual acuity, along with microperimetry, has been suggested as a functional measure to differentiate early and intermediate stages of dry AMD.

Quantitative CSF is another visual function measure that is distinct from VA. This approach uses an active-learning algorithm to measure CSF across multiple frequencies. Quantitative CSF can identify subtle visual function deficits that may be unrecognized with other methods. Wai et al[49] recently showed, using quantitative CSF, that CSF was significantly reduced in eyes with maculopathies in patients with good VA. These various functional tests should be further explored in combination, because combining multiple functional end points into a "cumulative end point" may increase the reliability of visual function assessment and provide an improved visual function outcome measure.

Recently, the ReCLAIM phase I Trial tested MTP-131, also known as elamipretide. This tetrapeptide reduces reactive oxygen species in the mitochondria, the location of greatest reactive oxygen species production, and stabilizes cardiolipin, a major lipid that is unique to mitochondrial membranes. In the open label phase I trial assessing MTP-131 applied by repeated subcutaneous injections in patients with intermediate AMD and GA, LLVA improved in patients with intermediate AMD by 5.6 letters ($P = 0.006$) and the measured GA change corresponded to a similar LLVA improvement of 5.4 letters ($P = 0.025$) after 24 weeks of treatment. Dark adaptation was also measured and was improved in $> 33\%$ of eyes when examined at $\geq 2$ visits. Interestingly, best-corrected VA also improved in patients with intermediate AMD by 3.58 letters ($P = 0.025$) and in nonfoveal GA by 4.6 letters ($P = 0.003$). These results suggest that both rod and cone function are influenced by MTP-131. Importantly, the phase I study highlights the potential of LLVA and dark adaptometry as functional end points when evaluating drug efficacy in intermediate AMD or GA, although approaches to reduce the relatively large test-retest variability will need to be addressed. Further validation of functional end points that can accurately reflect visual function and disease progression would enable clinical trials to test the therapeutic potential of drugs at earlier disease stages.

The results of ReCLAIM-1 were sufficiently promising to warrant a randomized prospective current phase II trial (ReCLAIM-2).[50] However, at the May 21, 2022 American Society of Retina Specialists Clinical Trials at the Summit meeting, Stealth announced that ReCLAIM-2 did not meet its primary end points of mean change in LLVA and GA progression. However, elamipretide decreased the decline of the photoreceptor ellipsoid zone layer ($P < 0.01$), an important indicator of photoreceptor loss, and showed a $>$ 2-line improvement in LLVA ($P = 0.04$) in patients with GA at week 48.

As new functional and imaging modalities emerge, the use of multimodal imaging, or the use of several different imaging modalities, combined with functional tests, will help to define the AMD phenotype beyond our standard clinical descriptions. Although classic AMD changes such as drusen are not sufficiently predictive of visual function to serve as a surrogate biomarker, intensive investigation for other findings is ongoing, as summarized by Terheyden et al.[51] This refinement will improve our ability to detect disease progression and treatment response. New modalities such as swept-source OCT, OCT angiography, adaptive optics, and adaptive optics-OCT may help to refine our AMD phenotypes and identify new imaging biomarkers that predict disease progression and treatment response. The settings and protocols of these imaging modalities will need to be optimized and integrated with functional assessments

of vision. However, the realities of patient tolerance during any clinical trial, time constraints, and financial limitations will be factors that guide the selection of imaging modalities in future clinical trials.

## Preclinical Considerations for Future Clinical Trials

Slowing GA enlargement presents several disadvantages as a primary end point in clinical trials testing new drugs for dry AMD. Patients with GA, as the late stage of dry AMD, suffer from irreversible tissue injury and loss of photoreceptors, RPE, and choriocapillaris.[52] As a result, the potential for visual recovery is limited. If a drug becomes FDA approved, its benefit might be limited to those patients without GA that involves the fovea. Conceptually, the factors causing disease onset or progression may be different from the major contributors of late-stage GA. Thus, the benefit of any drug for GA may not be effective for earlier stage disease. Alternatively, the etiologic pathways driving GA may be multiple. If true, then the benefit of a single treatment, while effectively influencing the intended dysregulated pathway, may not be beneficial because other disease-contributing processes overwhelm its treatment benefit.[53] By resolving these shortcomings in AMD pathogenesis, therapy can be directed toward the most pathogenic signals at the appropriate disease stage.

The lack of success with the phase III CHROMA and SPECTRI anti-factor D trials might be explained by these scientific concerns rather than clinical design criticisms. What if complement activity via the alternative pathway, for example, is most pathogenic in early disease, but less so in GA? With this scenario, lampalizumab might be effective in early stages of AMD and ineffective in slowing GA enlargement. What if another pathogenic pathway, such as the inflammasome, mitochondrial dysfunction, impaired autophagy, or lipid dysregulation is the predominant pathogenic signal during GA? With this scenario, lampalizumab would likely not be effective. Finally, what if multiple pathogenic pathways, including complement, are major pathogenic factors in GA? Multidrug treatment that includes lampalizumab would likely be more effective than lampalizumab alone.

As mentioned previously, our understanding of AMD pathobiology is based on epidemiologic, genetic, epigenetic, pharmacologic and clinical trials, and preclinical studies. However, at present, scientists and clinicians do not communicate to the extent needed to accelerate getting effective treatments into the clinic. Basic research meetings on AMD are rarely attended by clinicians. Likewise, few basic scientists attend clinical meetings on AMD. Furthermore, the vast majority of clinical trials are conducted by physicians in clinical practice who interact sparingly with basic researchers. Likewise, few meetings occur between scientists in industry with those in academia. The details of industry sponsored clinical trials are not available to outside scientists to analyze. Finally, current funding agencies are not designed to enable large, collaborative initiatives that would integrate large, multidimensional approaches to solve the gaps in AMD pathobiology that will help design effective treatment strategies. Overall, improved communication between clinicians and scientists would enhance the translation of scientific understanding with treatment that can enter the clinic.

The incomplete understanding of AMD pathobiology is perhaps illustrated by the controversial role of *HTRA1* in AMD. *HtrA Serine Peptidase 1* has received significant focus since genetic variations have been strongly linked to AMD risk. As a result, the phase I GALLEGO clinical trial assessed the safety of intravitreal anti-*HTRA1*. This humanized monoclonal antibody binds and neutralizes *HTRA1* activity. None of the 28 patients with GA who received monthly intravitreal anti-*HTRA1* had significant adverse effects.[54] The phase II GALLEGO trial is ongoing. Anti-*HTRA1* or sham-injected patients with GA are being randomized to receive either intravitreal anti-*HTRA1* or sham injection every 4 or every 8 weeks until week 76. Recently, Williams et al[55] recently reported that the function of *HTRA1* is important to maintain RPE-Bruch membrane integrity. This group found that patients with the high-risk genetic variation had reduced *HTRA1*, which impaired maintenance of the RPE-Bruch membrane interaction. They concluded that *HTRA1* augmentation, rather than inhibition, should be considered for an AMD treatment.[55]

With GA as a widely accepted functional end point surrogate, animal models have not fully reproduced GA to the extent that is needed for preclinical testing in a candidate drug's journey to human clinical trial. The current GA animal models are not topographically limited, but instead tend to be pan-retinal in distribution. Importantly, the models are limited to a single underlying pathologic pathway and may not represent the full scope of GA pathophysiology. However, several recent mice models have shown GA-like features, and although not completely comprehensive, they can provide a model for preclinical drug assessment.[56–59] The duration needed to develop GA can be an impediment.[58] Improvement in animal models of GA would enhance our ability to determine whether a candidate drug will transition to a human clinical trial.

## Future Directions for Dry AMD Treatment

Besides effective clinical trial design, further scientific understanding of AMD pathobiology will likely improve clinical trial success. The National Eye Institute's AMD pathobiology group concluded that accelerated treatment for AMD will rely on addressing 3 key unanswered questions.[60] First, what are the major pathogenic signals and what is their prioritized rank based on pathogenic contribution? Second, do these major pathways interact with one another? Finally, at what stage of AMD are they most pathogenic? To gain this understanding, improved access to human tissue, including high-quality, well-phenotyped AMD globes, aqueous, vitreous, blood, and urine samples from AMD and age-matched control patients is needed for research. The National Centralized Repository for

Alzheimer's disease provides a template. Currently, this registry has accumulated nearly 680 000 patient samples of blood, brain tissue, cerebral spinal fluid, and associated data that are available for Alzheimer's disease research.

Given the complex, multifactorial etiology of AMD, it is likely that different drugs targeting different pathogenic pathways will be needed at different disease stages. Alternatively, several different drugs that target the most pathogenic pathways might be needed for each AMD stage. Patients have different genetic profiles that establish disease risk. Currently, all the genetic variants have been associated with advanced AMD without separating GA from neovascular disease. The risk alleles that separate risk for GA from neovascular AMD would help with treatment design. It is also unclear which genetic variants are associated with early or intermediate AMD risk. Understanding this might help in understanding how to target treatment for early or intermediate AMD. Likewise, the different environmental influences such as smoking, sunlight exposure, diet, and other unknown factors on the epigenome and the epigenome's impact in driving AMD will need to be clarified and considered in the treatment. Currently, identifying a reliable, effective, and practical test that reflects visual function for all stages of AMD is a topic of intense investigation and is essential for future trials, not only in GA, but also for earlier disease stages. Ultimately, a personalized approach for treating patients with AMD that targets the major pathogenic pathways that are influenced by these genetic and epigenetic factors at each disease stage may be needed.

## Footnotes and Disclosures

Originally received: May 4, 2022.
Final revision: August 12, 2022.
Accepted: August 15, 2022.
Available online: August 19, 2022. Manuscript no. XOPS-D-22-00102R2.

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Disclosure(s):

All authors have completed and submitted the ICMJE disclosures form.

The author(s) have made the following disclosure(s): E.K.: Employee — Character Biosciences Inc., a biotechnology company working in the dry AMD therapeutic area; Vice President — Drug Discovery.

K.C.: Financial support — Novartis Pharma AG, NGM Biopharmaceuticals Inc., Gyroscope, Annexon Biosciences, Genentech/Roche, IVERIC Bio, Boehringer Ingelheim; Consultant — AbbVie, Adverum, Annexon, Cognition Therapeutics, Endogena, EyeBio, Genentech, Inc./Roche, Gyroscope, Heidelberg Engineering, Johnson & Johnson, Merck, NGM Biopharmaceuticals Inc., Novartis Pharma AG, Ocular Therapeutix, ReNeuron, Retrotope, Ribomic; Honoraria — Roche/Genentech; Participation — Adverum Biotechnologies—DSMB; Share — EyeBio.

J.T.H.: Financial support — Scientific Advisory Board, Bayer Pharmaceuticals, Consultant — Evergreen Inc., Character Biosciences Inc., Cirrus Pharmaceuticals, Seeing Medicine Inc., NanoRetina, Inc.; Participation — SAB for Character Biosciences, Seeing Medicine, and Cirrus Therapeutics; Leadership — SAB for Foundation Fighting Blindness, SAB for Ryan AMD RIMR group; Shares — Character Biosciences and Cirrus.

The other authors have no proprietary or commercial interest in any materials discussed in this article.

Supported by unrestricted grant from Research to Prevent Blindness (New York City, NY) to the Wilmer Eye Institute. Supported by the Robert B. Welch MD Professorship in Ophthalmology (J.T.H.). The funding organizations had no role in the design or conduct of this research.

HUMAN SUBJECTS: No human subjects were included in this study. This is a retrospective study using de-identified subject details. Informed consent was not obtained.

No animal subjects were included in this study.

Author Contributions:

Conception and design: Abidi, Kerrar, Csaky, Handa

Analysis and interpretation: Abidi, Kerrar, Csaky, Handa

Data collection: Abidi, Kerrar, Csaky, Handa

Obtained funding: N/A

Overall responsibility: Abidi, Kerrar, Csaky, Handa

Abbreviations and Acronyms:
**AMD** = Age-related macular degeneration; **FDA** = Food and Drug Administration; **GA** = geographic atrophy; ***HTRA1*** = *HtrA Serine Peptidase 1*; **LLVA** = low luminance visual acuity; **CSF** = contrast sensitivity; **RPE** = retinal pigment epithelium; **VA** = visual acuity.

Keywords:
Clinical trial, Complement, Geographic atrophy, Non-neovascular age-related macular degeneration.

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## References

1. Wong WL, Su X, Li X, 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:e106—e116.
2. Pennington KL, DeAngelis MM. Epidemiology of age-related macular degeneration (AMD): associations with cardiovascular disease phenotypes and lipid factors. *Eye Vis (Lond)*. 2016;3:34.
3. Friedman DS, O'Colmain BJ, Munoz B, et al. Prevalence of age-related macular degeneration in the United States. *Arch Ophthalmol*. 2004;122:564—572.
4. Chew EY, Clemons TE, Agron E, et al. Ten-year follow-up of age-related macular degeneration in the age-related eye disease study: AREDS report no. 36. *JAMA Ophthalmol*. 2014;132:272—277.
5. Virgili G, Michelessi M, Parodi MB, et al. Laser treatment of drusen to prevent progression to advanced age-related macular

degeneration. *Cochrane Database Syst Rev*. 2015;10: CD006537.
6. Sallo FB, Rechtman E, Peto T, et al. Functional aspects of drusen regression in age-related macular degeneration. *Br J Ophthalmol*. 2009;93:1345−1350.
7. Boyer DS, Schmidt-Erfurth U, van Lookeren Campagne M, et al. The pathophysiology of geographic atrophy secondary to age-related macular degeneration and the complement pathway as a therapeutic target. *Retina*. 2017;37:819−835.
8. Csaky K, Ferris III F, Chew EY, et al. Report from the NEI/FDA endpoints workshop on age-related macular degeneration and inherited retinal diseases. *Invest Ophthalmol Vis Sci*. 2017;58:3456−3463.
9. Shen LL, Sun M, Ahluwalia A, et al. Geographic atrophy growth is strongly related to lesion perimeter: unifying effects of lesion area, number, and circularity on growth. *Ophthalmol Retina*. 2021;5:868−878.
10. Yehoshua Z, Rosenfeld PJ, Gregori G, et al. Progression of geographic atrophy in age-related macular degeneration imaged with spectral domain optical coherence tomography. *Ophthalmology*. 2011;118:679−686.
11. Fritsche LG, Igl W, Bailey JN, et al. A large genome-wide association study of age-related macular degeneration highlights contributions of rare and common variants. *Nat Genet*. 2016;48:134−143.
12. Klein RJ, Zeiss C, Chew EY, et al. Complement factor H polymorphism in age-related macular degeneration. *Science*. 2005;308:385−389.
13. Edwards AO, Ritter III R, Abel KJ, et al. Complement factor H polymorphism and age-related macular degeneration. *Science*. 2005;308:421−424.
14. Hageman GS, Anderson DH, Johnson LV, et al. A common haplotype in the complement regulatory gene factor H (HF1/CFH) predisposes individuals to age-related macular degeneration. *Proc Natl Acad Sci USA*. 2005;102:7227−7232.
15. Haines JL, Hauser MA, Schmidt S, et al. Complement factor H variant increases the risk of age-related macular degeneration. *Science*. 2005;308:419−421.
16. Rivera A, Fisher SA, Fritsche LG, et al. Hypothetical LOC387715 is a second major susceptibility gene for age-related macular degeneration, contributing independently of complement factor H to disease risk. *Hum Mol Genet*. 2005;14:3227−3236.
17. Jakobsdottir J, Conley YP, Weeks DE, et al. Susceptibility genes for age-related maculopathy on chromosome 10q26. *Am J Hum Genet*. 2005;77:389−407.
18. Christen WG, Glynn RJ, Manson JE, et al. A prospective study of cigarette smoking and risk of age-related macular degeneration in men. *JAMA*. 1996;276:1147−1151.
19. Delcourt C, Diaz JL, Ponton-Sanchez A, Papoz L. Smoking and age-related macular degeneration. The POLA Study. Pathologies Oculaires Liees a l'Age. *Arch Ophthalmol*. 1998;116:1031−1035.
20. Klein R, Klein BE, Linton KL, DeMets DL. The beaver dam eye study: the relation of age-related maculopathy to smoking. *Am J Epidemiol*. 1993;137:190−200.
21. Seddon JM, Willett WC, Speizer FE, Hankinson SE. A prospective study of cigarette smoking and age-related macular degeneration in women. *JAMA*. 1996;276:1141−1146.
22. Vingerling JR, Hofman A, Grobbee DE, de Jong PT. Age-related macular degeneration and smoking. The Rotterdam Study. *Arch Ophthalmol*. 1996;114:1193−1196.
23. Talhout R, Schulz T, Florek E, et al. Hazardous compounds in tobacco smoke. *Int J Environ Res Public Health*. 2011;8: 613−628.
24. Foronjy R, D'Armiento J. The effect of cigarette smoke-derived oxidants on the inflammatory response of the lung. *Clin Appl Immunol Rev*. 2006;6:53−72.
25. Poyton RO, Ball KA, Castello PR. Mitochondrial generation of free radicals and hypoxic signaling. *Trends Endocrinol Metab*. 2009;20:332−340.
26. Karunadharma PP, Nordgaard CL, Olsen TW, Ferrington DA. Mitochondrial DNA damage as a potential mechanism for age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2010;51:5470−5479.
27. Nordgaard CL, Berg KM, Kapphahn RJ, et al. Proteomics of the retinal pigment epithelium reveals altered protein expression at progressive stages of age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2006;47:815−822.
28. Terluk MR, Kapphahn RJ, Soukup LM, et al. Investigating mitochondria as a target for treating age-related macular degeneration. *J Neurosci*. 2015;35:7304−7311.
29. Yaspan BL, Williams DF, Holz FG, et al. Targeting factor D of the alternative complement pathway reduces geographic atrophy progression secondary to age-related macular degeneration. *Sci Transl Med*. 2017;9:eaaf1443.
30. Holz FG, Sadda SR, Busbee B, 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;136: 666−677.
31. Soulika AM, Holland MC, Sfyroera G, et al. Compstatin inhibits complement activation by binding to the beta-chain of complement factor 3. *Mol Immunol*. 2006;43: 2023−2029.
32. Qu H, Ricklin D, Bai H, et al. New analogs of the clinical complement inhibitor compstatin with subnanomolar affinity and enhanced pharmacokinetic properties. *Immunobiology*. 2013;218:496−505.
33. Liao DS, Grossi FV, El Mehdi D, et al. Complement C3 inhibitor pegcetacoplan for geographic atrophy secondary to age-related macular degeneration: a randomized phase 2 trial. *Ophthalmology*. 2020;127:186−195.
34. Biogen. Biogen and Eisai to discontinue phase 3 ENGAGE and EMERGE trials of aducanumab in alzheimer's disease. https://investors.biogen.com/news-releases/news-release-details/biogen-and-eisai-discontinue-phase-3-engage-and-emerge-trials.
35. Budd Haeberlein S, Aisen PS, Barkhof F, et al. Two randomized phase 3 studies of aducanumab in early Alzheimer's disease. *J Prev Alzheimers Dis*. 2022;9:197−210.
36. Jaffe GJ, Westby K, Csaky KG, et al. C5 inhibitor avacincaptad pegol for geographic atrophy due to age-related macular degeneration: a randomized pivotal phase 2/3 trial. *Ophthalmology*. 2021;128:576−586.
37. Yehoshua Z, de Amorim Garcia Filho CA, Nunes RP, et al. Systemic complement inhibition with eculizumab for geographic atrophy in age-related macular degeneration: the COMPLETE study. *Ophthalmology*. 2014;121:693−701.
38. Heier J, Wykoff C, Singh R, et al. Society. Efficacy of intravitreal pegcetacoplan in geographic atrophy: results from the DERBY and OAKS trials. https://investors.apellis.com/static-files/fe6d8c27-e1b2-4c87-b77f-aa5cb249bacf. Accessed September 30, 2021.
39. US National Library of Medicine. A study of lampalizumab intravitreal injections administered every two weeks or every four weeks to participants with geographic atrophy. https://clinicaltrials.gov/ct2/show/NCT02288559. Accessed February 19, 2019.

40. Curcio CA, Medeiros NE, Millican CL. Photoreceptor loss in age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 1996;37:1236−1249.
41. Zekavat SM, Sekimitsu S, Ye Y, et al. Photoreceptor layer thinning is an early biomarker for age-related macular degeneration: epidemiologic and genetic evidence from UK Biobank OCT data. *Ophthalmology*. 2022;129:694−707.
42. Cocce KJ, Stinnett SS, Luhmann UFO, et al. Visual function metrics in early and intermediate dry age-related macular degeneration for use as clinical trial endpoints. *Am J Ophthalmol*. 2018;189:127−138.
43. Owsley C, McGwin Jr G, Jackson GR, et al. Cone- and rod-mediated dark adaptation impairment in age-related maculopathy. *Ophthalmology*. 2007;114:1728−1735.
44. Owsley C, McGwin Jr G, Clark ME, et al. Delayed rod-mediated dark adaptation is a functional biomarker for incident early age-related macular degeneration. *Ophthalmology*. 2016;123:344−351.
45. Ou WC, Lesmes LA, Christie AH, et al. Normal- and low-luminance automated quantitative contrast sensitivity assessment in eyes with age-related macular degeneration. *Am J Ophthalmol*. 2021;226:148−155.
46. Chen KG, Alvarez JA, Yazdanie M, et al. Longitudinal study of dark adaptation as a functional outcome measure for age-related macular degeneration. *Ophthalmology*. 2019;126:856−865.
47. Sunness JS, Rubin GS, Broman A, et al. Low luminance visual dysfunction as a predictor of subsequent visual acuity loss from geographic atrophy in age-related macular degeneration. *Ophthalmology*. 2008;115:1480−1488.
48. Puell MC, Barrio AR, Palomo-Alvarez C, et al. Impaired mesopic visual acuity in eyes with early age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2012;53:7310−7314.
49. Wai KM, Vingopoulos F, Garg I, et al. Contrast sensitivity function in patients with macular disease and good visual acuity. *Br J Ophthalmol*. 2022;106:839−844.
50. Allingham MJ, Mettu PS, Cousins SW. Phase 1 clinical trial of elamipretide in intermediate age-related macular degeneration and high-risk drusen: ReCLAIM high-risk drusen study. *Ophthalmol Sci*. 2022;2:100095.
51. Terheyden JH, Schmitz-Valckenberg S, Crabb DP, et al. Use of composite end points in early and intermediate age-related macular degeneration clinical trials: state-of-the-art and future directions. *Ophthalmologica*. 2021;244:387−395.
52. Fleckenstein M, Mitchell P, Freund KB, et al. The progression of geographic atrophy secondary to age-related macular degeneration. *Ophthalmology*. 2018;125:369−390.
53. Sunness JS, Rubin GS, Applegate CA, et al. Visual function abnormalities and prognosis in eyes with age-related geographic atrophy of the macula and good visual acuity. *Ophthalmology*. 1997;104:1677−1691.
54. Khanani AM, Hershberger VS, Pieramici DJ, et al. Phase 1 study of the anti-HtrA1 antibody-binding fragment FHTR2163 in geographic atrophy secondary to age-related macular degeneration. *Am J Ophthalmol*. 2021;232:49−57.
55. Williams BL, Seager NA, Gardiner JD, et al. Chromosome 10q26-driven age-related macular degeneration is associated with reduced levels of *HTRA1* in human retinal pigment epithelium. *Proc Natl Acad Sci USA*. 2021;118:e2103617118.
56. Bhutto IA, Ogura S, Baldeosingh R, et al. An acute injury model for the phenotypic characteristics of geographic atrophy. *Invest Ophthalmol Vis Sci*. 2018;59:AMD143−AMD151.
57. Ibbett P, Goverdhan SV, Pipi E, et al. A lasered mouse model of retinal degeneration displays progressive outer retinal pathology providing insights into early geographic atrophy. *Sci Rep*. 2019;9:7475.
58. Ebrahimi KB, Cano M, Rhee J, et al. Oxidative stress induces an interactive decline in Wnt and Nrf2 signaling in degenerating retinal pigment epithelium. *Antioxid Redox Signal*. 2018;29:389−407.
59. Cheng SY, Cipi J, Ma S, et al. Altered photoreceptor metabolism in mouse causes late stage age-related macular degeneration-like pathologies. *Proc Natl Acad Sci USA*. 2020;117:13094−13104.
60. Handa JT, Bowes Rickman C, Dick AD, et al. A systems biology approach towards understanding and treating non-neovascular age-related macular degeneration. *Nat Commun*. 2019;10:3347.