Efficacy and safety of avacincaptad pegol in patients with geographic atrophy (GATHER2): 12-month results from a randomised, double-masked, phase 3 trial

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Summary

Background Geographic atrophy is an advanced form of dry age-related macular degeneration that can lead to irreversible vision loss and high burden of disease. We aimed to assess efficacy and safety of avacincaptad pegol 2 mg in reducing geographic atrophy lesion growth.

Methods GATHER2 is a randomised, double-masked, sham-controlled, 24-month, phase 3 trial across 205 retina clinics, research hospitals, and academic institutions globally. To be eligible, patients had to be aged 50 years or older with non-centrepoint-involving geographic atrophy and best corrected visual acuity between 20/25 and 20/320 in the study eye. Eligible patients were randomly assigned (1:1) to monthly avacincaptad pegol 2 mg administered as a 100 µL intravitreal injection or sham for the first 12 months. Randomisation was performed using an interactive response technology system with stratification by factors known to be of prognostic importance in age-related macular degeneration. Patients, investigators, study centre staff, sponsor personnel, and data analysts were masked to treatment allocation. The primary endpoint was geographic atrophy lesion size measured by fundus autofluorescence at baseline, month 6, and month 12. Efficacy and safety analyses were done in the modified intention-to-treat and safety populations, respectively. This trial is registered with ClinicalTrials.gov, NCT04435366.

Findings Between June 22, 2020, and July 23, 2021, 1422 patients were screened for eligibility, of whom 448 were enrolled and randomly assigned to avacincaptad pegol 2 mg (n=225) or sham (n=223). One patient in the sham group did not receive study treatment and was excluded from analyses. There were 154 (68%) female patients and 71 (32%) male patients in the avacincaptad pegol 2 mg group, and 156 (70%) female patients and 66 (30%) male patients in the sham group. From baseline to month 12, the mean rate of square-root-transformed geographic atrophy area growth was 0·336 mm/year (SE 0·032) with avacincaptad pegol 2 mg and 0·392 mm/year (0·033) with sham, a difference in growth of 0·056 mm/year (95% CI 0·016–0·096; p=0·0064), representing a 14% difference between the avacincaptad pegol 2 mg group and the sham group. Ocular treatment-emergent adverse events in the study eye occurred in 110 (49%) patients in the avacincaptad pegol 2 mg group and 83 (37%) in the sham group. There were no endophthalmitis, intraocular inflammation, or ischaemic optic neuropathy events over 12 months. To month 12, macular neovascularisation in the study eye occurred in 15 (7%) patients in the avacincaptad pegol 2 mg group and nine (4%) in the sham group, with exudative macular neovascularisation occurring in 11 (5%) in the avacincaptad pegol 2 mg group and seven (3%) in the sham group.

Interpretation Monthly avacincaptad pegol 2 mg was well tolerated and showed significantly slower geographic atrophy growth over 12 months than sham treatment, suggesting that avacincaptad pegol might slow disease progression and potentially change the trajectory of disease for patients with geographic atrophy.

Funding Iveric Bio, An Astellas Company.

Introduction

Geographic atrophy is the advanced form of age-related macular degeneration.[1] On the basis of meta-analyses, geographic atrophy is estimated to affect up to 5 million individuals globally.[2] Geographic atrophy is characterised by the loss of photoreceptors, retinal pigment epithelium, and choriocapillaris, and progression over time might lead to substantial, irreversible central vision loss.[3,4] Individuals with geographic atrophy have decreased visual function, often associated with loss of independence, mobility, and quality of life.[5–7] Until 2023, there were no therapies approved by the US Food and Drug Administration (FDA) to prevent the development of geographic atrophy or to reduce its progression.[8–10]

The pathophysiology of geographic atrophy is multifactorial and not fully understood; however, overactivation of complement cascade-mediated inflammation has been attributed to age-related macular

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See Comment page 1396

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See Online for appendix

Research in context

Evidence before this study

The pathogenesis of geographic atrophy is multifactorial, with changes in homeostasis due to oxidative damage, chronic inflammation, excessive accumulation of lipofuscin, and overactivation of the complement system leading to the degeneration of the retinal pigment epithelium, the choriocapillaris, and photoreceptors. The complement system is implicated on the basis of several lines of evidence, including genetic, immunohistochemical, and preclinical findings. Complement component 5 (C5) is an attractive therapeutic target for geographic atrophy because inhibition of C5 prevents the formation of key terminal fragments of the complement system, C5a and C5b, potentially reducing inflammation and cell death. We conducted a PubMed search on Dec 15, 2022, for studies published in English from Dec 15, 2007, using the terms "(geographic atrophy)" AND "(complement)", which identified 25 reports with the "clinical trial" filter for article type. These studies (phase 1, 2, and 3, and post-hoc analyses of these studies) evaluated the effect of inhibition of various components of the complement system on the growth of geographic atrophy. In addition, studies were included that evaluated polymorphisms of the complement system and the effect of nutritional supplements on patients with these polymorphisms.

Added value of this study

Avacincaptad pegol is the first inhibitor of complement C5 to have met its primary objective in two randomised, double-masked, sham-controlled clinical trials. In GATHER1 and GATHER2, intravitreal avacincaptad pegol 2 mg significantly slowed geographic atrophy growth over 12 months. The results of GATHER2 show that the growth of geographic atrophy, regardless of the type of analysis (either square root transformation or observed, assuming constant growth rate or not), was slower with avacincaptad pegol 2 mg compared with sham treatment. Furthermore, avacincaptad pegol 2 mg was shown to be well tolerated over 12 months, with no events of intraocular inflammation, endophthalmitis, ischaemic optic neuropathy, or occlusive vasculitis reported in the study eye.

Implications of all the available evidence

Primary results from GATHER2 support the hypothesis that inhibition of the complement system might slow the progression of geographic atrophy. With the few treatments available for patients with geographic atrophy, avacincaptad pegol has the potential to provide eye care professionals and their patients with a treatment that slows the growth of geographic atrophy lesions. Reducing geographic atrophy lesion growth and slowing progression of disease might help patients maintain their independence, mobility, and quality of life.

degeneration pathogenesis, and dysregulation of the complement system has been implicated in geographic atrophy on the basis of several lines of evidence, including genetic, immunohistochemistry, and preclinical findings.[11,12] Complement component 5 (C5) acts near the terminal end of the complement system, promotes inflammation and cell death, and is enriched in immunohistochemically stained drusen.[11,13,14] Avacincaptad pegol (IZERVAY; Iveric Bio, An Astellas Company, Parsippany, NJ, USA) was approved by the FDA in August, 2023, for the treatment of geographic atrophy secondary to age-related macular degeneration.[10] Avacincaptad pegol, a pegylated ribonucleic acid aptamer, is a specific inhibitor of complement C5 that might be able to slow geographic atrophy progression by preventing the production of terminal, active C5 cleavage products (C5a and C5b).[15] By inhibiting C5, the upstream complement system continues uninterrupted, which might have potential benefits, such as preserving the neuroprotective and anti-inflammatory effects of C3 and C3a, compared with inhibition earlier in the cascade.[11,13–17] Avacincaptad pegol was previously evaluated in the randomised, double-masked, sham-controlled phase 2/3 GATHER1 study (NCT02686658). The primary objectives were met for both the avacincaptad pegol 2 mg and 4 mg groups. Compared with the sham groups, avacincaptad pegol 2 mg resulted in an absolute difference of 0·110 mm (95% CI 0·030–0·190; p=0·007), representing a 27% reduction, and avacincaptad pegol 4 mg in an absolute difference of 0·124 mm (0·038–0·209; p=0·005), representing a 28% reduction, in mean change in geographic atrophy area over 12 months (square root transformed), as measured by fundus autofluorescence.[15] Avacincaptad pegol showed continued reduction in the progression of geographic atrophy lesion growth versus sham over 18 months.[18] Treatment was well tolerated over 12 months and 18 months following monthly intravitreal administration of avacincaptad pegol at both doses.[15,18] Given the favourable benefit–risk profile seen in GATHER1 and the lower adverse event rate observed with the avacincaptad pegol 2 mg dose than the 4 mg dose, the phase 3 GATHER2 study was designed with the aim of evaluating the efficacy and safety of intravitreal injections of avacincaptad pegol 2 mg versus sham in patients with geographic atrophy. Results from the first 12 months of the 24-month GATHER2 study are reported here.

Methods

Study design

GATHER2 is a randomised, double-masked, sham-controlled phase 3 trial in which patients were enrolled at

205 retina clinics, research hospitals, and academic institutions globally (appendix pp 2–9). The study adhered to the tenets of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. The appropriate ethics committee or institutional review board at each study centre approved the protocol (appendix p 94). An independent data monitoring committee reviewed patient safety data during the trial (appendix p 91). The study protocol and details of amendments to the study protocol are in the appendix (pp 21, 30). This study is ongoing.

Patients

Eligible patients were aged 50 years or older with non-centrepoint-involving geographic atrophy, with a Snellen best corrected visual acuity (BCVA) between 20/25 (80 Early Treatment Diabetic Retinopathy Study [ETDRS] letters) and 20/320 (25 ETDRS letters) in the study eye. The geographic atrophy lesion had to be, in part, within 1500 µm from the centre of the fovea, with a total area of 2·5–17·5 mm² (1–7 disc areas), as determined by screening fundus autofluorescence images. For multifocal lesions, one or more lesions had to be at least 1·25 mm² (0·5 disc areas). Patients were ineligible if they had macular atrophy secondary to any condition other than age-related macular degeneration in either eye; receipt of any previous treatment for age-related macular degeneration or any previous intravitreal treatment for any indication in either eye, apart from oral vitamin or mineral supplements; or any presence of macular neovascularisation in either eye (appendix pp 10–11). Informed written consent was obtained from all patients.

Randomisation and masking

On day 1 of the study, eligible patients were randomly assigned (1:1) to monthly avacincaptad pegol 2 mg or sham. At month 12, randomisation was repeated for patients receiving avacincaptad pegol 2 mg, with these patients randomly assigned (1:1) to either continue receiving monthly avacincaptad pegol 2 mg or to receive avacincaptad pegol 2 mg every other month through to month 23 (appendix p 12). All patients receiving sham on day 1 continued receiving sham throughout the study (appendix p 22). Year 2 results will be reported once the study is completed. To maintain masking in year 2, patients who were randomly assigned to receive avacincaptad pegol 2 mg every other month will receive sham in alternative months when avacincaptad pegol 2 mg is not given. The final follow-up study visit was at month 24. Randomisation was performed by an independent vendor using an interactive response technology system with stratification based on factors known to be of prognostic importance in age-related macular degeneration: baseline visual acuity less than 50 ETDRS letters (20/100 Snellen equivalent) versus 50 or more ETDRS letters; size of baseline geographic atrophy (<4 disc areas *vs* ≥4 disc areas); and pattern of fundus autofluorescence at the junctional zone of geographic atrophy (none or focal *vs* banded or diffuse). Masking remained from the time of randomisation until the database lock at month 12, when select sponsor roles were unmasked to treatment assignments for results interpretation. All others, patients, investigators, assessors, and sponsor roles involved in the conduct of the ongoing study remained masked until final database lock at month 24 (appendix p 13).

Procedures

Patients assigned to the avacincaptad pegol 2 mg group received avacincaptad pegol 2 mg administered as a 100 µL intravitreal injection monthly from day 1 through to month 11, with the final study visit for year 1 at month 12. Similarly, patients assigned to the sham group received sham injections monthly from day 1 through to month 11 (appendix p 13). Patients were monitored every month from day 1 through to month 12. Key ocular assessments were performed at prespecified timepoints. BCVA, intraocular pressure, full ophthalmological examination, and optical coherence tomography were completed monthly. Low-luminance BCVA (LL-BCVA), colour fundus photography, and fundus autofluorescence were completed every 6 months. An independent and masked reading centre (the Duke Reading Centre, Durham, NC, USA) assessed all ocular images. Sex was patient reported and coded as sex (male or female) on the case report form.

Outcomes

The prespecified primary endpoint was geographic atrophy lesion size measured by fundus autofluorescence at at least three timepoints (baseline, month 6, and month 12), which was analysed using a slope analysis of square-root-transformed data, a request by the FDA, to determine the mean rate of geographic atrophy growth from baseline to month 12 (see appendix pp 17–18 for details on image acquisition and geographic atrophy area measurement).

To assess consistency in efficacy, the mean rate of geographic atrophy growth via slope analysis of observed data (prespecified secondary analysis) and the mean change in geographic atrophy area using a point analysis of observed data (post hoc) from baseline to month 12 were also performed.

Prespecified secondary endpoints were change in BCVA and LL-BCVA from baseline to month 12 (ETDRS letters). Further prespecified supportive outcomes are listed in the appendix (pp 130–131).

A post-hoc subgroup analysis was performed, in which subgroups were defined on the basis of patient and lesion baseline characteristics, to evaluate consistency of treatment response over 12 months, using observed data.

A post-hoc exploratory time-to-event analysis evaluated the reduction in persistent vision loss with avacincaptad

pegol 2 mg versus sham over 12 months. Persistent vision loss was defined as a loss of 15 or more ETDRS letters in BCVA from baseline measured at any two consecutive visits up to month 12 and represents a doubling of the visual angle, which is considered clinically relevant by clinicians and the FDA. Consecutive vision loss ensures the vision loss is persistent and not a temporary fluctuation.

Safety endpoints included adverse events, vital signs, ophthalmological variables, 12-lead electrocardiogram (ECG), and laboratory variables. We used the classification macular neovascularisation, which is further divided into exudative macular neovascularisation and non-exudative macular neovascularisation, and is a newer classification that is more descriptive than choroidal neovascularisation, because neovascularisation does not necessarily originate from the choroid. Exudative macular neovascularisation presents with subretinal or intraretinal fluid, whereas non-exudative macular neovascularisation is characterised by macular neovascularisation in the absence of fluid or macular neovascularisation that is not visible, but both a double-layer sign (shallow, irregular retinal pigment epithelium elevation) and sub-retinal pigment epithelium fluid are present.[8,19,20] For patients who developed macular neovascularisation in the study eye, with diagnosis confirmed by the Duke Reading Center, macular neovascularisation was treated with either ranibizumab or aflibercept per their label, and patients remained in the trial. Before the year 1 database lock, the masked review of optical coherence tomography images was conducted by the Cleveland Clinic Cole Eye Institute CORE Reading Center (Cleveland, OH, USA) to establish the number of patients with macular neovascularisation versus peripapillary choroidal neovascularisation and the number with exudative versus non-exudative macular neovascularisation (appendix p 19).

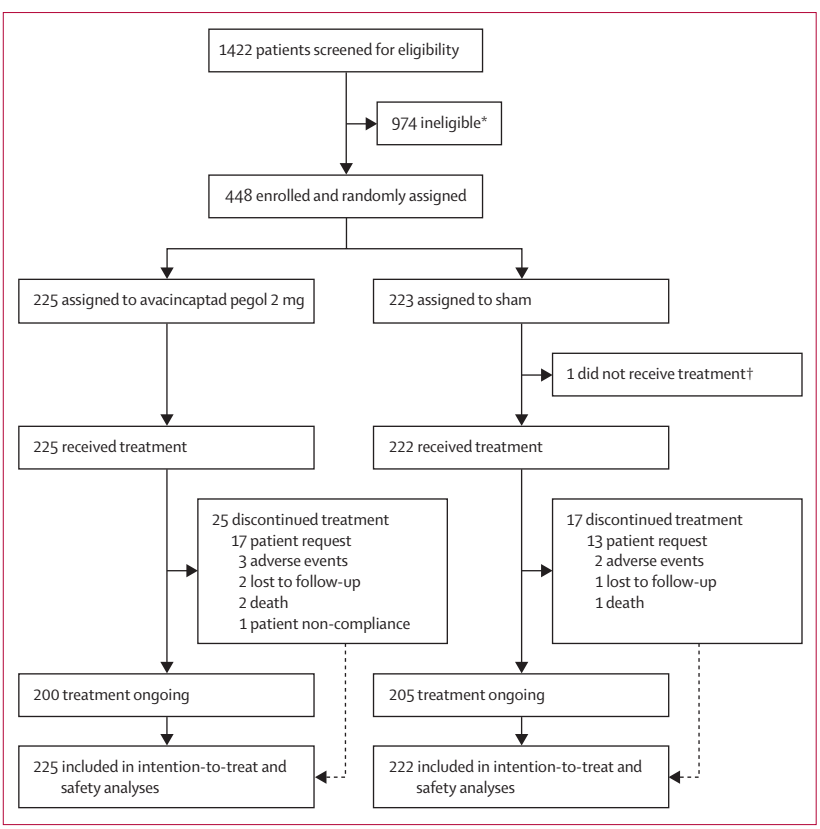

Figure 1: **Trial profile**
*The most common (>95%) reason for ineligibility was related to the patient not meeting specific ophthalmological inclusion criteria or meeting exclusion criteria. †Due to withdrawal of consent before the baseline visit.

Statistical analysis

GATHER2 had a target sample size of 400 patients, determined from the 12-month results of GATHER1. For the primary endpoint, this sample size provided 97% power at a two-sided 5% significance level to detect at least a 0·11 mm slower mean geographic atrophy growth rate over 12 months compared with sham. All efficacy analyses were conducted in the modified intention-to-treat population, which consisted of all randomly assigned patients who received at least one dose of the study drug.

A mixed model for repeated measures was used to assess differences between the treatment groups in rate of growth of the square root of geographic atrophy area (slope) over 12 months. This analysis provided valid estimates if the missing data mechanism fulfilled the missing-at-random assumption; moreover, sensitivity analyses were performed to assess the potential magnitude and direction of the impact of missing data (appendix pp 14–16).

A similar analysis was conducted using the observed geographic atrophy area measurement. Baseline characteristics and demographic information are presented with descriptive statistics using the modified intention-to-treat population. All safety analyses were performed in the safety population, which included all patients who received at least one dose of the study drug. Safety measures were calculated based only on observed cases. For analyses of BCVA and LL-BCVA, a mixed model for repeated measures was used to assess the differences between treatment groups in mean change in BCVA and LL-BCVA (ETDRS letters) from baseline to the month 12 visit. Analyses of supportive outcomes were conducted with descriptive intent only (appendix pp 144–146). Statistical analyses were done using SAS 9 (version 9.4). This study is registered at ClinicalTrials.gov, NCT04435366.

Role of the funding source

The funder of the study participated in the design and conduct of the study, including data collection, data management, data analysis, and data interpretation, and writing of the report.

Results

Between June 22, 2020, and July 23, 2021, 1422 patients were screened for eligibility, of whom 448 were enrolled

and randomly assigned to monthly avacincaptad pegol 2 mg (n=225) or sham (n=223), including one patient assigned to the sham group who was not treated with an investigational product (figure 1). The most common (>95%) reasons for being ineligible on screening were related to the patient not meeting specific ophthalmic inclusion criteria or meeting ophthalmic exclusion criteria, which included geographic atrophy lesions involving the foveal centrepoint, total geographic atrophy area size not meeting requirements, and evidence of macular neovascularisation in either eye. There were 154 (68%) female patients and 71 (32%) male patients in the avacincaptad pegol 2 mg group, and 156 (70%) female patients and 66 (30%) male patients in the sham group. The proportion of patients who completed the study through to month 12 was similar between groups (200 [89%] in the avacincaptad pegol 2 mg group and 205 [92%] in the sham group). The most common reasons for early study discontinuation in both treatment groups was patient withdrawal (figure 1). The proportion of patients with at least one major protocol deviation was similar in both groups, with 45 (20%) patients each. The most common major protocol deviations (>2% in either group) were missed assessments, violation of eligibility criteria, deviation from informed consent form procedure, missed visits, and treatment not per protocol. Demographics were well balanced between the two treatment groups (table 1).

The last patient visit for year 1 was on July 25, 2022. The prespecified primary objective of a reduction in mean rate of geographic atrophy growth (slope) at 12 months was met. From baseline to month 12, the mean rate of square-root-transformed geographic atrophy area growth (slope) was 0·336 mm/year (SE 0·032) with avacincaptad pegol 2 mg versus 0·392 mm/year (0·033) with sham treatment, an absolute difference of 0·056 mm/year (95% CI 0·016–0·096; p=0·0064), representing a 14% difference in geographic atrophy area growth between the avacincaptad pegol 2 mg group and the sham group (figure 2A; appendix p 25).

The mean rate of growth (slope) using observed data was similar to results obtained for the prespecified primary endpoint. From baseline to month 12, the mean rate of observed geographic atrophy area growth (slope) was 1·745 mm²/year (SE 0·202) with avacincaptad pegol 2 mg versus 2·121 mm²/year (0·207) with sham treatment, a difference of 0·376 mm²/year (95% CI 0·122–0·631; p=0·0039), representing an 18% difference in geographic atrophy area growth between the avacincaptad pegol 2 mg group and the sham group (figure 2B; appendix p 25).

The least-squares mean differences in BCVA and LL-BCVA between the avacincaptad pegol 2 mg group and the sham treatment group are shown in table 2.

Ocular treatment-emergent adverse events in the study eye occurred in 110 (49%) patients in the avacincaptad pegol 2 mg group and 83 (37%) in the sham group (table 3). The most reported (>2% in total patients) ocular treatment-emergent adverse events in the study eye were conjunctival haemorrhage, conjunctival hyperaemia, punctate keratitis, increased intraocular pressure, macular neovascularisation, dry eye, eye pain, vitreous detachment, and cataract (appendix p 26). Ocular serious adverse events in the study eye were reported in four patients: two (<1%) in the avacincaptad pegol 2 mg group developed macular neovascularisation, one (<1%) patient in the sham group developed macular neovascularisation, and one (<1%) patient in the sham group developed reduced visual acuity and transiently reduced visual acuity. No ocular serious adverse events were related to the injection procedure. The study drug was discontinued

	Avacincaptad pegol 2 mg group (n=225)	Sham group (n=222)
Age, years	77 (71–83)	77 (71–83)
Sex		
Female	154 (68%)	156 (70%)
Male	71 (32%)	66 (30%)
Race or ethnicity		
White	182 (81%)	186 (84%)
Asian	1 (<1%)	1 (<1%)
Black or African American	0	1 (<1%)
American Indian or Alaska Native	1 (<1%)	0
Other	10 (4%)	13 (6%)
Not reported	31 (14%)	21 (9%)
Hispanic or Latinx	27 (12%)	23 (10%)
Active smoker	106 (47%)	107 (48%)
Ocular characteristics		
Square root geographic atrophy area, mm*	2·64 (0·71)	2·71 (0·70)
Observed geographic atrophy area, mm²*	7·48 (4·00)	7·81 (3·89)
Bilateral geographic atrophy	212 (94%)	210 (95%)
Geographic atrophy lesion focality*		
Unifocal	47 (21%)	44 (20%)
Multifocal	178 (79%)	178 (80%)
Hyperautofluorescence pattern*		
Diffuse or banded	217 (96%)	218 (98%)
Focal or none	8 (4%)	4 (2%)
Lens status		
Phakic	102 (45%)	94 (42%)
Pseudophakic	123 (55%)	128 (58%)
BCVA, ETDRS letters*	70·9 (8·9)	71·6 (9·4)
LL-BCVA, ETDRS letters*	41·0 (19·7)	39·6 (19·6)

Age data are median (IQR). All other data are n (%) or mean (SD). Baseline was the last available measurement before the first administration of study drug. BCVA=best corrected visual acuity. ETDRS=Early Treatment Diabetic Retinopathy Study. LL-BCVA=low-luminance BCVA. *Study eye.

Table 1: **Demographics and baseline characteristics in the modified intention-to-treat population**

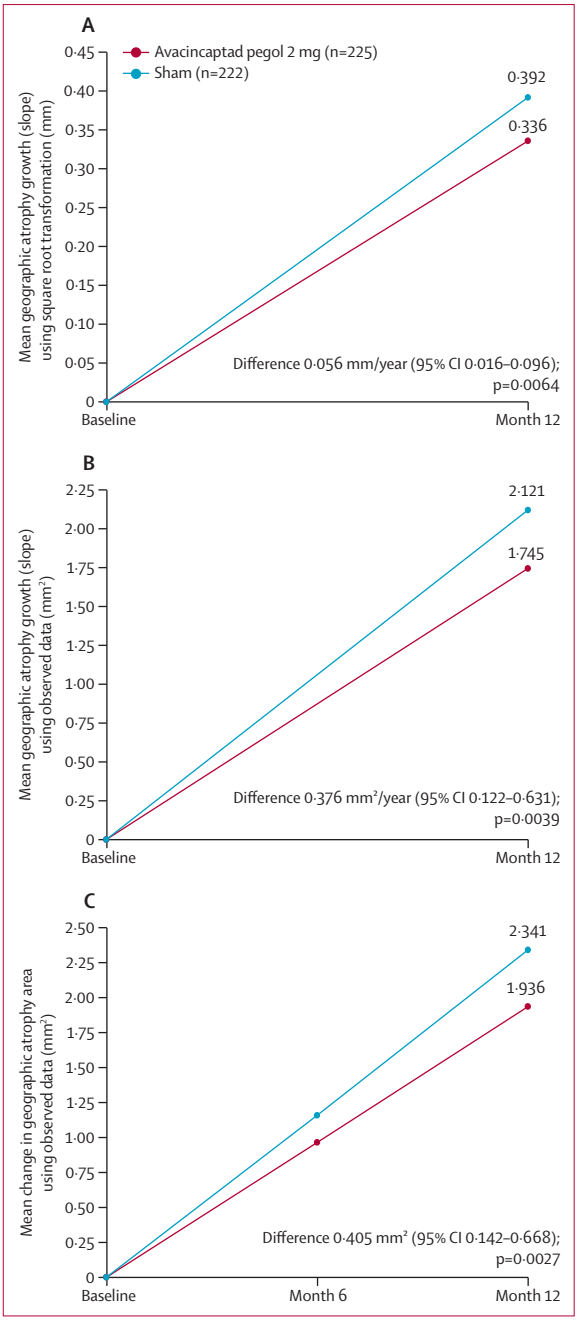

Figure 2: **Geographic atrophy growth over time at month 12**
(A) Primary analysis of the mean rate of growth in geographic atrophy area (slope) using square root transformation. Baseline geographic atrophy size and pattern on fundus autofluorescence were stratified at randomisation and the square root of the geographic atrophy area was used in the primary analysis. (B) Mean rate of growth in geographic atrophy area (slope) using observed data. (C) Mean change in geographic atrophy area (point analysis) using observed data. Data for all three charts were from mixed model for repeated measures analyses in the modified intention-to-treat population.

due to treatment-emergent adverse events in eight (2%) patients: six (3%) in the avacincaptad pegol 2 mg group and two (<1%) in the sham group. Of these eight patients, two in the avacincaptad pegol 2 mg group had ocular treatment-emergent adverse events leading to study drug discontinuation: vitreous detachment and increased intraocular pressure (related to injection procedure). No study-drug-related ocular or non-ocular treatment-emergent adverse events led to study drug discontinuation. There were no events of endophthalmitis, intraocular inflammation, or ischaemic optic neuropathy over 12 months in either treatment group.

21 (9%) patients in the avacincaptad pegol 2 mg group and two (<1%) in the sham group developed increased intraocular pressure in the study eye. Most events occurred after the injection, were transient, resolved the same day, and were considered related to injection procedure and not the study drug. To month 12, 15 (7%) patients in the avacincaptad pegol 2 mg group developed macular neovascularisation in the study eye (two of which were considered serious): 11 (5%) patients had exudative macular neovascularisation, one (<1%) had non-exudative macular neovascularisation, and three (1%) patients developed peripapillary choroidal neovascularisation. During this same period, nine (4%) sham-treated patients developed macular neovascularisation in the study eye (one of which was considered serious): seven (3%) patients had exudative macular neovascularisation and two (<1%) had peripapillary choroidal neovascularisation.

The incidence of non-ocular treatment-emergent adverse events was similar between the treatment groups: 125 (56%) patients in the avacincaptad pegol 2 mg group and 127 (57%) in the sham group (appendix p 27). Non-ocular treatment-emergent adverse events related to the injection procedure were uncommon (n=3; <1% across both groups), and none was determined to be related to the study drug by the investigator. Non-ocular serious treatment-emergent adverse events occurred in 29 (13%) patients in the avacincaptad pegol 2 mg group and 35 (16%) in the sham group (appendix p 28). There were three deaths (two in the avacincaptad pegol 2 mg group and one in the sham group) to month 12, none of which was determined by the investigator to be related to injection procedure or the study drug. Vital signs, laboratory parameters, and ECGs did not show any differences between the treatment groups or changes from baseline, and the results were consistent with this patient population (data not shown).

In a post-hoc analysis, the mean change in observed geographic atrophy area from baseline to month 12 was 1·936 mm² (SE 0·215) for avacincaptad pegol 2 mg and 2·341 mm² (0·221) for sham, a difference of 0·405 mm² (95% CI 0·142–0·668; p=0·0027), representing a 17% difference between the avacincaptad pegol 2 mg group and the sham group (figure 2C; appendix p 25).

The post-hoc subgroup analysis showed that the mean rate of observed geographic atrophy area growth (slope) was consistently lower for avacincaptad pegol 2 mg than for sham for all patient demographics and baseline disease characteristics analysed, including both male and female subgroups (appendix p 23).

In the post-hoc analysis of persistent vision loss, defined as the observed loss of 15 or more ETDRS letters from baseline measured at any two consecutive visits up to month 12, risk probability was 3·1% (95% CI 1·6–6·9) for avacincaptad pegol 2 mg versus 7·7% (5·0–12·6) for sham (hazard ratio 0·41 [95% CI 0·17–1·00]; logRank p=0·042; appendix p 24). Results of the sensitivity analyses of the impact of missing data are shown in the appendix (p 20).

Discussion

The primary objective of assessing the difference in geographic atrophy growth between avacincaptad pegol 2 mg and sham was met in the large, randomised, phase 3 GATHER2 study. Treatment with avacincaptad pegol 2 mg showed a significantly slower mean rate of geographic atrophy growth versus sham. Another pivotal study of avacincaptad pegol, GATHER1, independently showed a significant difference in geographic atrophy growth between avacincaptad pegol 2 mg and sham.[15] In GATHER2 at 12 months, there were no substantial differences in mean change in BCVA or LL-BCVA between treatment groups, which is not unexpected within the timeframe of clinical trials, because patients might temporarily compensate by using remaining islands of viable retinal tissue. However, at various timepoints, patients will eventually have a significant and persistent drop in visual acuity, which might be accounted for in the categorical analyses. Hence, an exploratory time-to-event analysis evaluating loss of 15 or more ETDRS letters from baseline over the first 12 months of treatment was conducted and signalled that the rate of persistent vision loss with avacincaptad pegol 2 mg versus sham was more than halved (hazard ratio 0·41). These results suggest that in eyes treated with avacincaptad pegol, it might be possible to modify the trajectory of disease, leading to preservation of the spared retina and lowering the risk of persistent vision loss. Based on the literature, progression rates for geographic atrophy can range from 0·53 mm²/year to 2·6 mm²/year, with a median of 1·78 mm²/year, and the rate of progression appears to be linear.[1,4] The geographic atrophy growth analysis using observed data from GATHER2 is consistent with findings from other clinical studies of geographic atrophy[4,21,22] and in clinical practice. Taken together, these results suggest that avacincaptad pegol 2 mg, which achieved the 12-month primary objective in two pivotal phase 3 studies, effectively slowed geographic atrophy growth, further corroborating the role of the complement pathway in the pathogenesis of geographic atrophy.

The safety profile of avacincaptad pegol 2 mg was consistent across the two studies: no new unexpected adverse events were identified in GATHER2 compared with GATHER1.[15] After 12 months of treatment with avacincaptad pegol 2 mg, no events of intraocular inflammation, endophthalmitis, ischaemic optic neuropathy, or occlusive vasculitis in the study eye were reported. The higher incidence of elevated intraocular pressure was expected with avacincaptad pegol 2 mg because the intraocular injection volume is 100 µL and most events were transient. These results were similar to GATHER1, with the exception of one patient with intraocular inflammation in the avacincaptad pegol 2 mg group at 12 months in GATHER1, which was mild, transient, and not related to the injection procedure or study drug.[18] In GATHER2 and GATHER1,[15] the incidence

	Least-squares mean		Absolute difference	95% CI*	p value
	Avacincaptad pegol 2 mg group (n=225)	Sham group (n=222)			
BCVA	1·34 (1·48)	0·96 (1·51)	0·38 (0·92)	−1·43 to 2·19	0·68
LL-BCVA	−4·35 (2·30)	−2·29 (2·36)	−2·06 (1·43)	−4·86 to 0·75	0·15

Data are least-squares mean (SE) unless otherwise stated. The baseline ETDRS BCVA score was the mean value of the screening and day 1 BCVA scores rounded up to the nearest integer if not already an integer. If either the screening or day 1 BCVA score was missing (including an invalid BCVA), the baseline BCVA was equal to the other, non-missing, value. Difference in least-squares means between groups was calculated as (avacincaptad pegol 2 mg) minus (sham). Positive difference favoured avacincaptad pegol. BCVA=best corrected visual acuity. ETDRS=Early Treatment Diabetic Retinopathy Study. LL-BCVA=low-luminance BCVA. MMRM=mixed model for repeated measures. *95% CIs for the absolute differences.

Table 2: **Mean change in BCVA and LL-BCVA (ETDRS letters) in the study eye from baseline to month 12 in the modified intention-to-treat population using MMRM analysis**

	Avacincaptad pegol 2 mg group (n=225)	Sham group (n=222)
Non-ocular treatment-emergent adverse events		
Treatment-emergent adverse events	125 (56%)	127 (57%)
Treatment-emergent adverse events related to injection procedure	2 (<1%)	1 (<1%)
Treatment-emergent adverse events related to study drug	0	0
Serious treatment-emergent adverse events	29 (13%)	35 (16%)
Severe treatment-emergent adverse events	31 (14%)	25 (11%)
Treatment-emergent adverse events leading to study drug discontinuation	4 (2%)	2 (<1%)
Ocular treatment-emergent adverse events		
Ocular treatment-emergent adverse events		
Study eye	110 (49%)	83 (37%)
Fellow eye	50 (22%)	42 (19%)
Serious ocular treatment-emergent adverse events		
Study eye	2 (<1%)	2 (<1%)
Fellow eye	0	0
Severe ocular treatment-emergent adverse events, study eye	5 (2%)	1 (<1%)
Ocular treatment-emergent adverse events related to injection procedure, study eye	63 (28%)	43 (19%)
Ocular treatment-emergent adverse events related to treatment, study eye	4 (2%)	2 (<1%)
Ocular treatment-emergent adverse events leading to study drug discontinuation, study eye	2 (<1%)	0
Endophthalmitis, study eye	0	0
Intraocular inflammation, study eye	0	0
Ischaemic optic neuropathy, study eye	0	0

Data are n (%).

Table 3: **Summary of treatment-emergent adverse events at month 12 in the safety population**

of serious ocular treatment-emergent adverse events in the study eye was low (two and zero, respectively), and no treatment-emergent adverse events leading to study drug discontinuation were assessed as related to avacincaptad pegol 2 mg over 12 months. Macular neovascularisation and geographic atrophy are not mutually exclusive entities of age-related macular degeneration and can appear in the same eye.[23,24] Unlike in the GATHER1 study, patients who developed macular neovascularisation in GATHER2 remained in the study and received treatment for macular neovascularisation. Similar to the GATHER1 study,[15] the incidence of macular neovascularisation in GATHER2 was higher with avacincaptad pegol 2 mg than with sham. Interestingly, new-onset macular neovascularisation has been reported in several clinical studies showing reduction in geographic atrophy growth with complement inhibition.[15,25–27] Several hypotheses exist for the occurrence of macular neovascularisation in eyes that have received therapies targeting the complement pathway.[27–30] For example, it is hypothesised that VEGF signalling plays a role in macular neovascularisation development; therefore, treating eyes with geographic atrophy might result in the continued production of VEGF in surviving cells, possibly resulting in higher macular neovascularisation rates versus untreated eyes.[27,29]

Limitations of the study include the length of follow-up, considering that geographic atrophy is a chronic disease; however, patients who completed the second year of GATHER2 and provide written informed consent will be enrolled in the ongoing open-label extension for an additional 18 months of treatment and safety monitoring in this chronic disease. In addition, macular neovascularisation and peripapillary choroidal neovascularisation were characterised on the basis of multimodal imaging, including optical coherence tomography and fundus autofluorescence, but not optical coherence tomography angiography. All the prespecified subgroups from the post-hoc analyses showed a favourable treatment effect consistent with the overall analysis, supporting generalisability of the trial results to the general patient population. Furthermore, GATHER2 enrolled patients with geographic atrophy without foveal involvement, which is reflective of earlier presentation in newly diagnosed patients with geographic atrophy;[31] therefore, results from this study are generalisable to this patient population.

In conclusion, the results of GATHER2 showed that monthly C5 inhibition with avacincaptad pegol 2 mg showed slower geographic atrophy growth compared with sham treatment and was well tolerated over 12 months of treatment. Although monthly injections can be a substantial burden to both patients and clinicians, the results of this study show that there is a treatment that can be used to slow the progression of the disease and the associated effect on the patient's vision. These data, together with the results of the GATHER1 study, suggest that avacincaptad pegol 2 mg might slow the progression of geographic atrophy.

Contributors

JC, LZ, HP, JT, and DD participated in the design of the study. AMK, SSP, GS, RT, CJD, DAE, JH, CCW, JSH, DRL, JM, JSN, VSS, PKK, and GJJ participated in advisory committees or as study investigators. GJJ graded images and oversaw the grading activities for the study. JC, LZ, HP, JT, and DD provided study oversight. All authors participated in data acquisition, research execution, or both. LZ and JT performed all statistical analysis. All authors participated in the analysis or interpretation of the data, or both. JC, LZ, HP, JT, and DD vouch for the data and analyses, and for the fidelity of this report to the study protocol and data analysis plan. LZ and JT accessed and verified the data in the study. All authors participated in the drafting and critical review of the study manuscript. All authors had full access to the data and made the final decision on all aspects of this publication, including the final responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

The second year of the GATHER2 study is currently ongoing; therefore, data sharing is not available at this time. However, the study protocol and statistical analysis plan are included in the appendix (pp 30, 125).

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