Randomized Trial to Evaluate Tandospirone in Geographic Atrophy Secondary to Age-Related Macular Degeneration: The GATE Study

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• PURPOSE: To determine the safety and efficacy of AL-8309B (tandospirone) in the management of patients with geographic atrophy (GA) secondary to age-related macular degeneration (AMD) and obtain standardized data on GA lesion growth progression.

• DESIGN: Prospective, controlled, double-masked, randomized, multicenter phase 3 clinical trial.

• METHODS: SETTING: Forty-eight clinical sites. PATIENTS: Patients with GA associated with AMD were enrolled. All patients were followed for a minimum of 30 months, and up to 36 months. INTERVENTION PROCEDURES: Patients were randomized (1:1:1) to receive AL-8309B ophthalmic solution 1.0%, 1.75%, or vehicle, administered as a twice-daily topical ocular drop. MAIN OUTCOME MEASURES: The primary efficacy endpoint was mean annualized lesion enlargement from baseline as assessed with fundus autofluorescence (FAF) imaging.

• RESULTS: A total of 768 eyes of 768 patients were enrolled and treated with AL-8309B 1.0% (n = 250), AL-8309B 1.75% (n = 258), or vehicle (n = 260). An increase in mean lesion size was observed in both the AL-8309B and vehicle treatment groups, and growth rates were similar in all treatment groups. Annualized lesion growth rates were 1.73, 1.76, and 1.71 mm^2 for AL-8309B 1.0%, AL-8309B 1.75%, and vehicle, respectively.

• CONCLUSIONS: AL-8309B 1.0% and 1.75% did not affect lesion growth in eyes with GA secondary to AMD. There were no clinically relevant safety issues identified for AL-8309B. The large natural history dataset from this study is a valuable repository for future comparisons. (Am J Ophthalmol 2015;160(6):1226–1234.

GEOGRAPHIC ATROPHY (GA) IS THE ADVANCED form of dry age-related macular degeneration (AMD), a progressive degenerative disease that is associated with severe visual impairment and enlargement of scotomas. The central field visual loss caused by GA is progressive, irreversible, and bilateral in the majority of patients.[1,2] AMD affects approximately 8 million people in the United States alone, with an annual incidence of almost 500 000, and is responsible for 20% of all the cases of severe vision loss in North America.[3–6] The prevalence of GA increases with age and approximately quadruples per decade beyond age 50. The estimated prevalence of GA in populations of European ancestry at 70 years of age is 0.7%, rising to 2.9% at 80 years of age and 11.3% at 90 years of age.[4] In the year 2040, the prevalence of GA in the overall population is expected to increase by 75%.[7]

Anatomically, GA is characterized by atrophy of the photoreceptors, retinal pigment epithelium (RPE), and choriocapillaris. Various changes that include thickening of the Bruch membrane and deposition of waste products, lipofuscin accumulation in the RPE, RPE hypopigmentation, and drusen formation underneath the RPE cell monolayer precede photoreceptor loss in GA. Large and confluent drusen represent a significant risk factor.[8]

GA pathogenesis is thought to be multifactorial; biochemical, histologic, and genetic studies have implicated several mechanisms, including oxidative damage, chronic inflammation, and excessive accumulation of lipofuscin. Several lines of evidence support the critical roles played by oxidative stress and inflammation in the development and progression of AMD. Oxidized proteins and protein adducts (eg, carboxyethylpyrrole) have been detected by proteomic analysis in drusen of eyes with AMD. Additionally, oxidation products detected by immunohistochemistry have been observed in the retina

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of eyes with advanced AMD and GA.[9–11] Epidemiologic studies in elderly patients have found that smoking is a risk factor, whereas a diet rich in antioxidants is a risk reduction factor for the development of AMD.[12,13] Lastly, the Age-Related Eye Disease Study (AREDS) showed that supplements containing antioxidant vitamins and zinc reduced the risk for progression of earlier stages of AMD, although the effect on GA was not studied.[14] Based on this body of evidence, drugs that have an antioxidant and/or neuroprotective role are strong candidates for GA therapy.

Currently, there are no approved treatments to prevent the worsening of GA or the associated decline in visual function. This treatment paucity is mainly owing to the lack of suitable molecular targets or animal models. Apart from general lifestyle advice (dietary, vitamins, etc), there are no specific interventions to slow or reverse progression from early AMD to late disease stages.[7] In addition, certain anti–vascular endothelial growth factor medications, used for the treatment of neovascular AMD, may in fact worsen the progression of GA, as studies in mice have shown that these treatments can interfere with the ocular vasculature and may be associated with RPE and choroidal atrophy.[15]

In a preclinical study, where a model of retinal degeneration was used to test a number of neuroprotective agents, 5-HT1A agonists were among the most potent agents evaluated.[16,17] Although 5-HT1A agonists have primarily been used to treat anxiety and depression, this class of compounds is known for its cell-protective activity following traumatic brain injury,[18,19] in excitotoxicity induced by N-methyl-D-aspartate,[20] and in a variety of central nervous system ischemia models.[21–23] Because these studies suggested a possible neuroprotective role of 5-HT1a receptor activation, a search was initiated for a clinical-stage 5-HT1a agonist. Subsequently, a formulation (AL-8309B) for potential topical ocular use in the management of GA was developed. In albino and pigmented rats subjected to a severe acute photo-oxidative stress, AL-8309B protected photoreceptors and RPE cells in a dose-dependent manner.[16]

Based on the preclinical data, the Geographic Atrophy Treatment Evaluation (GATE) phase 3 clinical trial program (NCT00890097) was initiated to evaluate the safety and efficacy of AL-8309B in patients with GA. In the present report, we describe the safety and efficacy of AL-8309B when given topically to treat GA associated with non-neovascular AMD.

METHODS

THE GATE STUDY WAS A PROSPECTIVE, CONTROLLED, double-masked, randomized (1:1:1), multicenter phase 3 interventional clinical trial designed to determine the safety and efficacy of AL-8309B ophthalmic solution vs vehicle administered as a twice-daily topical eye drop to treat GA secondary to AMD. The study was performed in compliance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice and multiple Institutional Review Boards (IRBs) including a central IRB (Sterling IRB) and institutional and local IRBs (country-specific). Patients provided signed informed consent. This was the first-in-human proof-of-concept study conducted to establish efficacy relative to vehicle. Investigational New Drug (IND) number 101095 was registered in the clinical trials database of the National Institute of Health (ClinicalTrials.gov Identifier: NCT00890097).

Included in the study were patients who were aged 55 years or older with GA secondary to AMD with no evidence of choroidal neovascularization in the study eye, those with a well-demarcated area of atrophy (if multifocal, at least 1 focal lesion must have been equal to or larger than 1.25 mm^2), and a total lesion size of less than or equal to 20 mm^2. The study eye also had to have hyperautofluorescence adjacent to the area of atrophy, a best-corrected visual acuity (BCVA) of 35 letters (20/200 Snellen) or better, and clear ocular media and adequate pupillary dilation to allow high-quality photographic imaging.

Excluded from the study were patients with ocular disease other than nonexudative AMD in the study eye that may confound assessment of GA lesions, or that may affect central visual acuity (eg, branch retinal vein occlusion, diabetic retinopathy, and uveitis); a history of cataract surgery in either eye within the past 3 months of screening or a history or evidence of serious ocular trauma or intraocular surgery (laser in situ keratomileusis, keratoplasty) in either eye within the past 6 months of screening; and current or previous use of serotonin receptor agonists, selective serotonin reuptake inhibitors, selective serotonin/epinephrine reuptake inhibitors, monoamine oxidase inhibitors, and triptans within 30 days of screening.

The first patient was enrolled April 28, 2009 and enrollment ended in December 2009. The study was completed on May 31, 2012. Sequential patient numbers were randomly assigned to treatment groups according to a randomization schedule generated by the Alcon statistical programming group. The randomization was blocked within center to ensure balanced treatment groups within each center. Patients were randomized at visit 2 (day 0) and had follow-up visits to the clinic at weeks 2, 4, and 12 and every 12 weeks thereafter for the study duration. The patients and investigators, as well as all study and Alcon personnel who had contact with investigators or patients, were masked with regard to treatment assignments while the study was in progress. Patients were to be followed for up to 36 months with a minimum follow-up for all patients of 30 months. However, as per the

TABLE 1. Demographics and Ocular Characteristics of Patients Involved in the Geographic Atrophy Treatment Evaluation Clinical Trial

Characteristic	AL-8309B 1.0% N = 252	AL-8309B 1.75% N = 259	Vehicle N = 261	Total N = 772
Male, n/N (%)	122/252 (48)	97/259 (37)	114/261 (44)	333/772 (43)
Age (y), mean (SD)	77.9 (8.0)	78.3 (7.7)	78.8 (7.1)	78.3 (7.6)
Race, n/N (%), white	243/252 (96)	253/259 (98)	251/261 (96)	747/772 (97)
Iris color, n (%), blue	81 (32)	102 (39)	92 (35)	275 (36)
Study eye, n (%), right	142 (56)	138 (53)	148 (57)	428 (55)
Months from diagnosis				
n	250	258	259	767
Mean (SD)	42.4 (41.7)	44.7 (43.5)	45.1 (42.7)	44.1 (42.6)
Baseline lesion size (mm^2), mean (SD)	7.4 (4.6)	7.5 (4.4)	7.6 (4.5)	7.5 (4.5)

AL-8309B 1.75% = AL-8309B ophthalmic solution, 1.75%; AL-8309B 1.0% = AL-8309B ophthalmic solution, 1.0%; Vehicle = AL-8309B ophthalmic solution vehicle.

Column header counts and denominators are the number of randomized patients.

recommendation from the Data Monitoring Committee (DMC) the study was discontinued after 600 patients had completed month 24 visit assessment, because the treatment was determined to be ineffective.

Both eyes (study eye and nonstudy eye) were dosed with study medication. If both eyes met the criteria, the eye with the best visual acuity at the screening visit (visit 1) was designated as the study eye. If both eyes met the criteria and had the same visual acuity at the screening visit (visit 1), the dominant eye was designated as the study eye. Patients instilled 1 drop of study medication into each eye twice daily with a dosing interval of approximately 12 h.

Confocal scanning laser ophthalmoscopy blue light fundus autofluorescence (FAF) was performed using HRAc, HRA2, or Spectralis (Heidelberg Engineering, Heidelberg, Germany). FAF and color fundus photography (CFP) images were collected at baseline and at minimum every 6 months for up to 36 months. Fluorescein angiograms (FAs) were collected at the screening visit only. Fluorescein angiography and CFP were performed with standard fundus cameras with a minimum resolution of 2000 × 2000 pixels. To minimize variability, certification of the assessment procedures and examiners at each investigative site occurred prior to any study eye image evaluation. Fluorescein angiographic, CFP, and FAF images were transmitted from study sites to the Duke Reading Center (central reading center) through a secure, web-based portal. Images were then assigned to trained Duke Reading Center or GRADE Reading Center readers, who independently assessed the FAs, CFPs, and FAF images for study eligibility and measured lesion size at study visits to determine lesion growth. Readers measured the atrophic lesion areas with semi-automated software (RegionFinder; Heidelberg Engineering, Heidelberg, Germany), as previously described.[24]

To monitor ocular safety, BCVA was assessed, as determined by the number of letters read on an Early Treatment Diabetic Retinopathy Study (ETDRS) chart. In addition, a complete ophthalmic examination was performed that included slit-lamp examination, dilated fundus examination by ophthalmoscopy, and intraocular pressure (IOP) measurement.

Four interim analyses were performed. The first interim analysis was performed to assess patient safety after ~200 patients had completed 6 months of follow-up. The second and third analyses were primarily administrative to allow for an assessment of the conditional power associated with the primary efficacy hypothesis. These 2 interim analyses were performed after ~600 evaluable patients had completed 12 and 18 months of follow-up, respectively. The fourth interim analysis was performed after all evaluable patients had completed 24 months of follow-up. At the final meeting, the DMC recommended the study be stopped for futility.

• **STATISTICAL ANALYSIS:** The primary efficacy endpoint was the mean annualized lesion growth rate from baseline, as assessed with FAF imaging. Lesion growth rate was defined as the change in lesion size from baseline to months 6, 12, 15, 18, 24, and 30. A longitudinal random-effects regression model (from a linear mixed model using an unstructured covariance matrix) was used to estimate the annualized lesion growth rate, taking into consideration that follow-up occurred over the 24-month period, after which the study was terminated. Secondary endpoints included mean BCVA change from baseline and mean changes from baseline in the near activity scores, distance activity, and vision-specific dependency subscales of the National Eye Institute 25-Item Visual Function

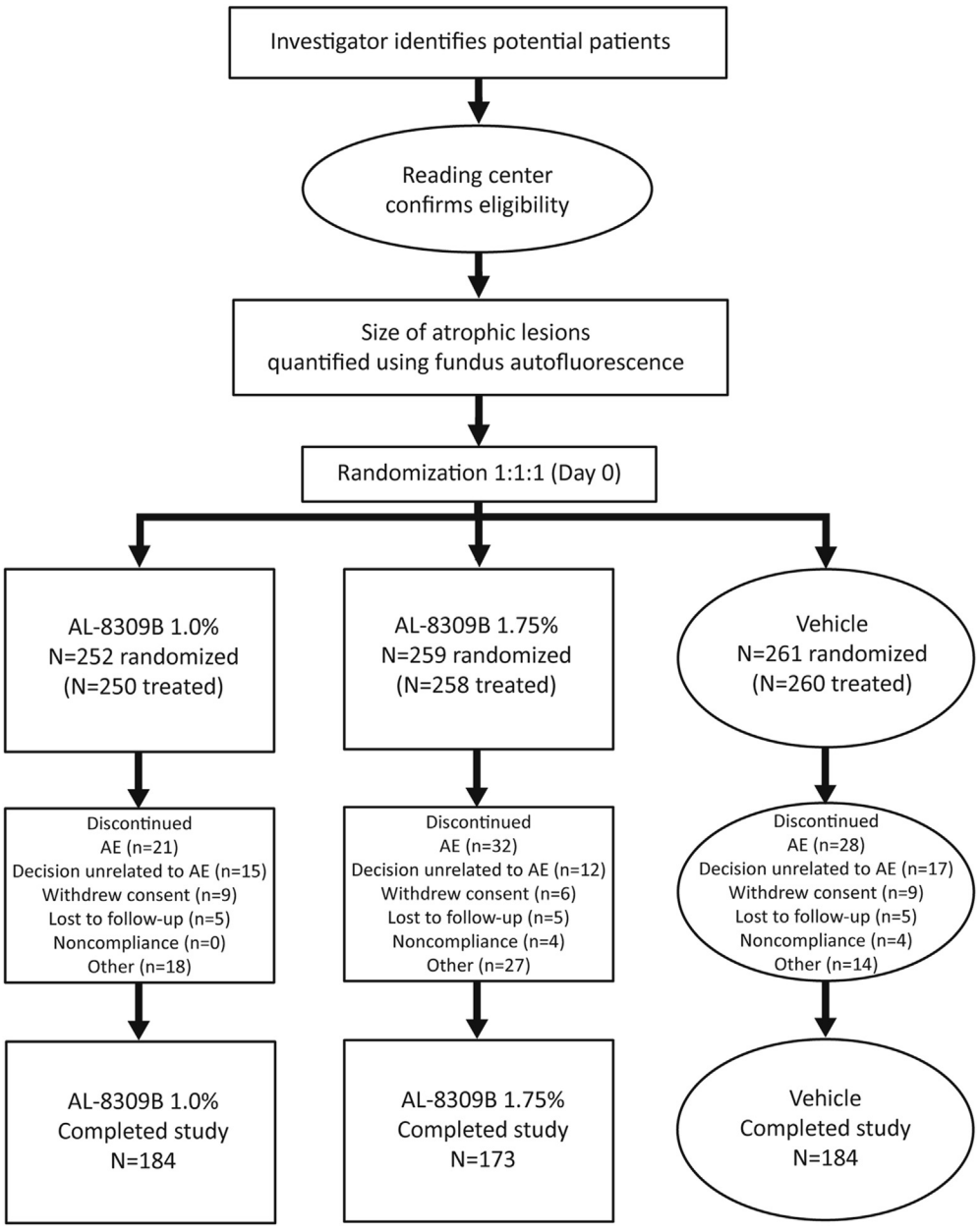

FIGURE 1. CONSORT flow diagram for patients involved in the Geographic Atrophy Treatment Evaluation (GATE) trial. Patient progress through the GATE trial is indicated in the diagram, including final N values for each study arm. AE, adverse event.

Questionnaire (NEI VFQ-25). The VFQ-25 data were not analyzed because of the early study termination. Statistics including number (N), mean, standard deviation, minimum, maximum, and quartiles were provided for the primary and secondary endpoints at each visit.

RESULTS

THE PATIENT DEMOGRAPHICS AND BASELINE CHARACTERistics are provided in Table 1. A total of 772 patients who met eligibility criteria (some of whom were active participants in an earlier natural history study, the Geographic Atrophy Progression [GAP] clinical trial; ClinicalTrials.gov identifier: NCT00599846) were enrolled at 48 global clinical sites. Of 772 randomized patients, 768 were treated (AL-8309B 1.0%, n = 250; AL-8309B 1.75%, n = 258; vehicle, n = 260) (Figure 1). Patient disposition is also provided in Figure 1. The majority of patients were white and the mean age was 78 years. In 55% of patients, the right eye was chosen as the study eye and the mean GA duration in the study eye, approximately 44 months, was similar among the 3 groups.

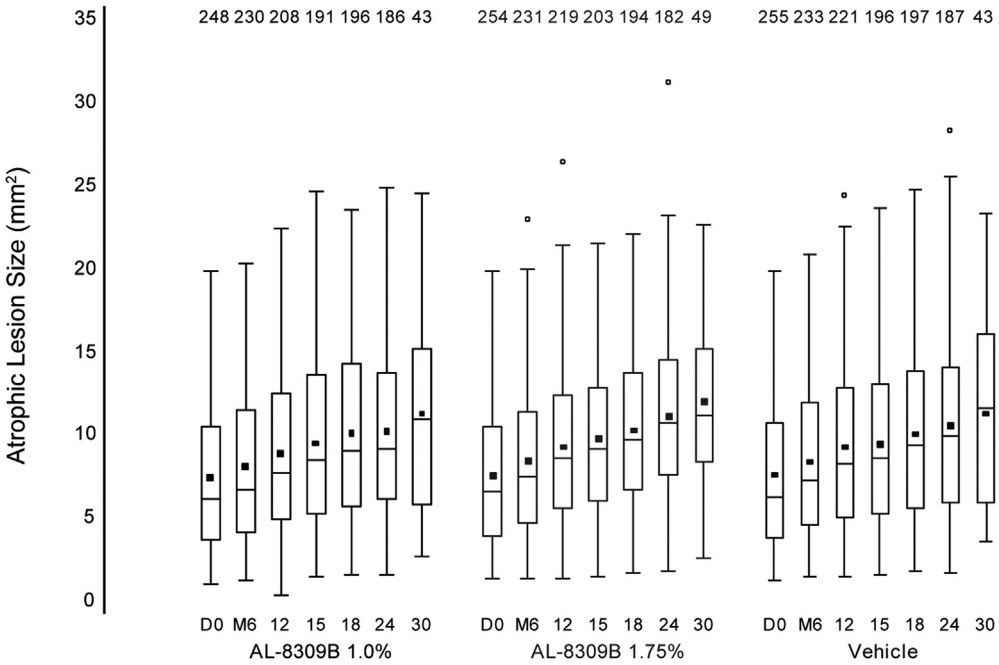

FIGURE 2. Lesion size distribution and change from baseline by visit in the study eye in the Geographic Atrophy Treatment Evaluation trial. Box plots show distribution (top) and change from baseline (bottom) of lesion size (mm^2) by visit in the study eye after treatment with AL-8309B vs vehicle. Counts are subjects with baseline and post-baseline data at the specified visit. D, day; M, month.

The mean total lesion size at baseline in the study eye was 7.4 mm^2 in the AL-8309B 1.0% group, 7.5 mm^2 in the AL-8309B 1.75% group, and 7.6 mm^2 in the vehicle group (Table 1). An increase in the mean lesion size was observed in both the AL-8309B and vehicle treatment groups (Figure 2) and was identical in patients treated with AL-8309B compared to those treated with vehicle (Figure 3). The annualized lesion growth rate for AL-8309B 1.0%, AL-8309B 1.75%, and vehicle was 1.73, 1.76, and 1.71 mm^2, respectively (Table 2).

There was a small decrease in mean study eye BCVA during the study (Figure 4). The BCVA change did not differ significantly among patients treated with AL-8309B compared to those that were treated with vehicle. The percentage of eyes with a 10-letter or greater decrease when treated with AL-8390B 1.0% and 1.75% was 30% and 29%, respectively, at month 24, and 38% and 35%, respectively, at month 30.

There were no clinically important differences among treatment groups in the frequency of ocular adverse events (AEs) based on individual system organ classes (Table 3). Common AEs (≥4% in any 1 treatment class) included reduced visual acuity, cataracts, eye irritation, eye pain, blepharitis, choroidal neovascularization, macular degeneration, blurred vision, and increased lacrimation (Table 3). These events were generally comparable among AL-8309B and vehicle treatment groups. However, AEs in the study eye were slightly more frequent for patients receiving AL-8309B 1.0% or 1.75% compared to vehicle for the following ocular AEs: eye irritation (8%, 10% vs 3%), eye pain (6%, 7% vs 3%), blepharitis (5%, 7% vs 3%), and increased lacrimation (3%, 6% vs 1%). Overall, AL-8309B had a favorable ocular safety profile with a serious adverse event (SAE) frequency of <1%.

DISCUSSION

IN THE CURRENT REPORT, WE ASSESSED THE EFFECT OF AL-8309B compared to placebo on the growth rate of GA lesions in eyes with AMD. The lesion growth rate was approximately 1.75 mm^2 per year, and did not differ, regardless of whether patients were treated with AL-8309B or vehicle. AL-8309B was generally tolerated, and there were few SAEs associated with its use.

We used GA lesion growth rate rather than visual acuity changes to monitor the therapeutic effect of AL-8309B. For some diseases, such as diabetic macular edema and neovascular AMD, central visual acuity loss is a useful biomarker of disease progression. Similarly, in eyes with GA that affects the central fovea, there may be significant associated central visual acuity loss that results from dense, irreversible scotomas. However, in eyes with foveal-sparing GA, there may be minimal effects on central visual acuity. Furthermore, BCVA does not correlate well with the size

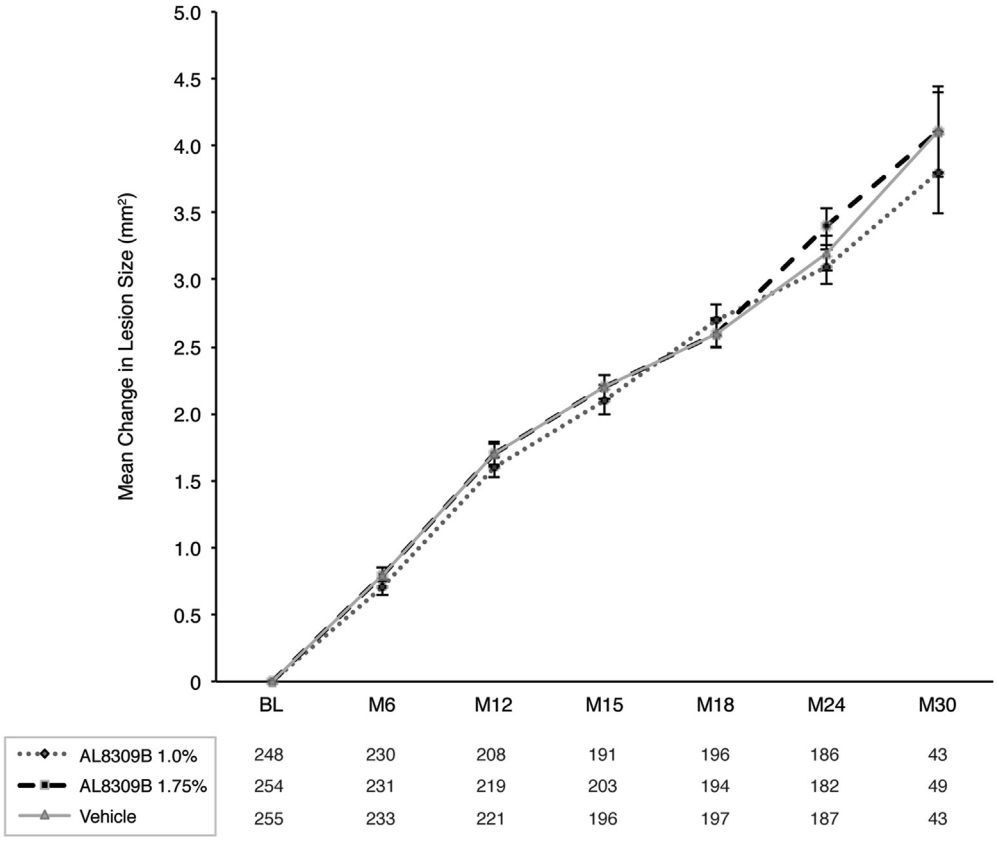

FIGURE 3. Mean change from baseline (BL) in lesion size in the study eye in the Geographic Atrophy Treatment Evaluation trial. Growth rate (mm^2, ± SE) of the lesion size with treatment of AL-8309B and vehicle. Lines connect the mean of the lesion size at each visit. Counts are subjects with baseline and post-baseline data at the specified visit. SE, standard error; M, month.

TABLE 2. Annualized Lesion Growth Rate After Treatment With AL-8309B or Vehicle in the Geographic Atrophy Treatment Evaluation Clinical Trial

	AL-8309B 1.0% N = 250	AL-8309B 1.75% N = 258	Vehicle N = 260
Mean (95% CI) yearly change from baseline	1.725 (1.595, 1.855)	1.758 (1.626, 1.890)	1.707 (1.585, 1.830)
Mean (95% CI) difference from vehicle	0.017 (−0.161, 0.196)	0.051 (−0.129, 0.231)	

AL-8309B 1.75% = AL-8309B ophthalmic solution, 1.75%; AL-8309B 1.0% = AL-8309B ophthalmic solution, 1.0%; CI = confidence interval; Vehicle = AL-8309B ophthalmic solution vehicle.

Column header counts are the number of randomized and treated patients.

Lesion sizes reported in mm^2.

Results estimated from a longitudinal random-effects regression model.

of a GA lesion; therefore, alternative clinical endpoints have been sought. For example, GA lesion growth rate (as was used in the present study), drusen, progression of intermediate to advanced AMD, reading speed, dark adaptation, microperimetry, and contrast sensitivity are alternate endpoints that are used to assess the anatomic and functional effects of GA disease progression.[25]

The observed annual growth rate in this study, approximately 1.75 mm^2, was slightly higher than that reported in the Fundus Autofluorescence Imaging in Age-Related Macular Degeneration (FAM) study (median 1.52 mm^2), which examined FAF patterns associated with GA and the impact on GA progression rates over time,[26] and in the Beaver Dam Eye Study, (6.4 mm^2 over 5 years, average

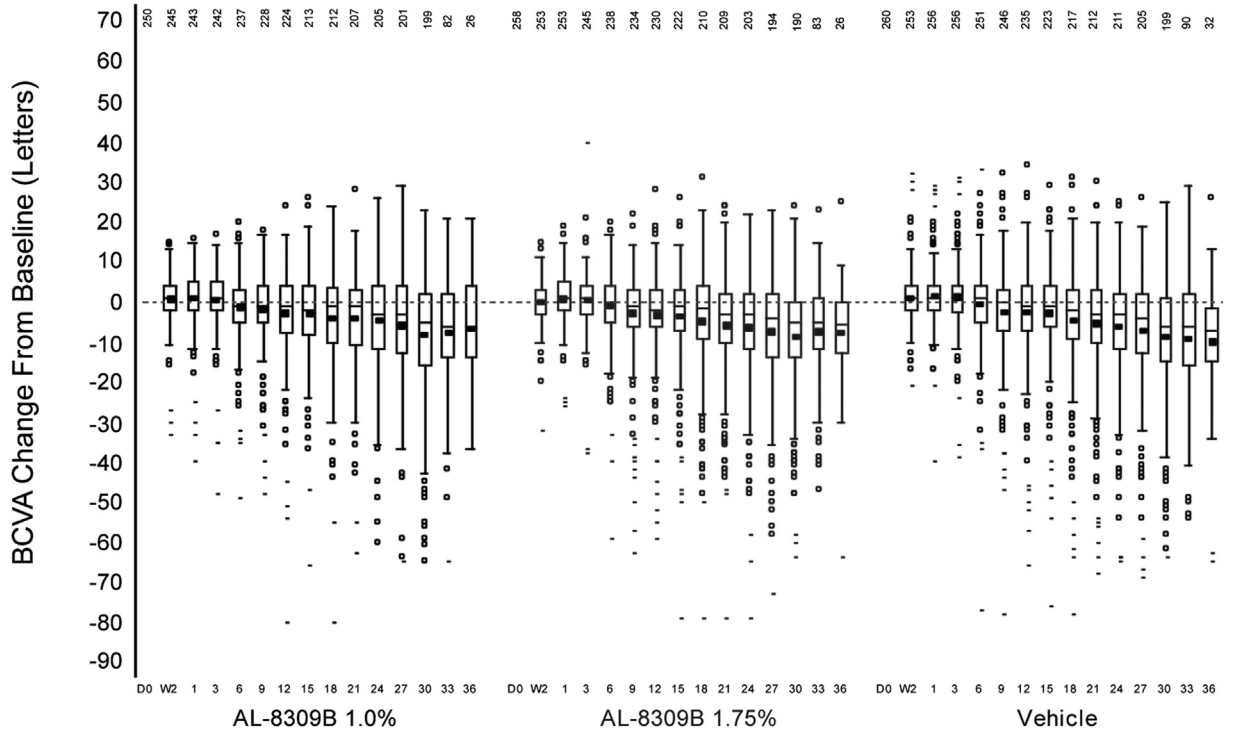

FIGURE 4. Distribution and change in best-corrected visual acuity (BCVA) from baseline after AL-8309B treatment vs vehicle in the Geographic Atrophy Treatment Evaluation trial. Box plots show the changes in BCVA in Early Treatment Diabetic Retinopathy Study (ETDRS) letters (top) and BCVA change from baseline (bottom) after treatment with AL-8309B vs vehicle. Counts are subjects with baseline and post-baseline data at the specified visit. D, day; W, week.

1.3 mm^2 per year), which examined the change in size and location of GA lesions.[1,3] In clinical studies, the GA growth rates vary widely among individuals and may range from 1.2 mm^2 to 2.8 mm^2 per year.[3] The reason for this variability is not understood, and may include inherent study population differences, different trial protocols (including different measurement methods), follow-up periods, or different genotype distributions for which the trial population is not specified or powered. This study is significant because the standardized follow-up and the comprehensive analysis in the absence of any therapeutic effects nonetheless provides robust GA natural history data that will inform future analyses of the correlation of GA lesion size, morphology, growth rate, and location with visual function.

For the primary study endpoint, given the similar growth rates between the treated and untreated eyes, the data suggest a lack of treatment effect by AL-8309B given in the topical formulation used in the study. The mean visual acuity change, a key secondary endpoint, was similar in all treatment groups, further supporting a lack of drug efficacy. Definitive reasons for the lack of efficacy within this study are unknown, but possible explanations include the following: the topical AL-8309B administration may not have provided adequate posterior segment drug delivery; tested doses may have been too low to exert a therapeutic effect; the drug may not have been administered during an optimal stage of disease; and/or the trial design was based on experimental animal models of degenerative disease, which may not reflect human GA pathogenesis. Furthermore, autofluorescence topography differs distinctly from the topography of age-related rod loss, suggesting that lipofuscin, a target of AL-8309B, may not induce RPE apoptosis.[27] The latter 2 points could have accounted for an inherent lack of drug treatment effect; the duration of the study and the high attrition rate may also have played a role in the lack of drug efficacy.

Endpoints that capture anatomic changes earlier may have helped identify more subtle lesion progression. Spectral-domain optical coherence tomography (SD OCT) can provide high-resolution cross-sectional anatomic images of relevant biological tissues such as the neurosensory retina and the choroid. In contrast, FAF offers en face imaging. However, SD OCT, which complements information obtained from FAF, and which may have provided insights into drug effect and longitudinal pathophysiology of GA, was not used in this study.[28] Furthermore, an analysis of drug effect on growth rate,

TABLE 3. Frequent Adverse Events in the Study Eye After Treatment With AL-8309B or Vehicle in the Geographic Atrophy Treatment Evaluation Clinical Trial

	AL-8309B 1.0% N = 250	AL-8309B 1.75% N = 258	Vehicle N = 260
Any ocular AEs in the study eye	166 (66)	172 (67)	157 (60)
Visual acuity reduced	81 (32)	82 (32)	85 (33)
Cataract	25 (10)	16 (6)	15 (6)
Eye irritation	19 (8)	27 (10)	7 (3)
Eye pain	14 (6)	18 (7)	9 (3)
Blepharitis	13 (5)	19 (7)	7 (3)
Choroidal neovascularization	10 (4)	12 (5)	10 (4)
Macular degeneration	9 (4)	15 (6)	8 (3)
Vision blurred	11 (4)	9 (3)	7 (3)
Lacrimation increased	8 (3)	15 (6)	2 (1)
Serious ocular AEs in the study eye, n (%)	0 (0)	3 (1)	4 (2)
Visual acuity reduced	0 (0)	1 (<1)	2 (1)
Cataract	0 (0)	0 (0)	1 (<1)
Macular edema	0 (0)	1 (<1)	0 (0)
Retinal detachment	0 (0)	1 (<1)	0 (0)
Hallucination, visual	0 (0)	0 (0)	1 (<1)

AEs = adverse events; AL-8309B 1.75% = AL-8309B ophthalmic solution, 1.75%; AL-8309B 1.0% = AL-8309B ophthalmic solution, 1.0%; Vehicle = AL-8309B ophthalmic solution vehicle.

Results are n (%).

Column header counts are the number of randomized and treated patients. A patient is counted at most once in each Medical Dictionary for Regulatory Activities system organ class or preferred term row. Only preferred terms occurring in at least 4% of 1 treatment group are presented for nonserious AEs.

stratified by GA lesion type, as determined by hyperautofluorescence pattern, number and location of lesions, genotype, and SD OCT characteristics, may have provided additional important information.

Currently, there are no approved treatments for patients with GA associated with AMD. In eyes with non-neovascular AMD, diverse causes of RPE cell toxicity have been identified.[29] Therefore, an agent such as AL-8309B, which targets a specific cell stressor such as oxidative injury, may not be sufficient to reverse or prevent the damage to the cells caused by other factors. Additional candidate factors currently being investigated include components of the complement system, which have been identified by genome-wide association studies.[3] The role of complement inhibition as a potential treatment for GA is supported by phase 2 results from the MAHALO study (NCT01229215) demonstrating that patients treated with lampalizumab (anti-factor D) had a significant reduction in the GA area enlargement at 18 months compared to placebo. In contrast, in the COMPLETE study, systemic complement inhibition by eculizumab inhibiting complement factor 5 did not decrease the growth rate of GA.[30] There are other clinical trial programs examining agents that block different steps in the complement cascade or act to preserve photoreceptor and RPE health.[3,7] Drug classes that maintain RPE and photoreceptor health by decreasing cell stress and enhancing cell survival remain important areas of investigation.[29] We hypothesize that combination therapy with agents to target different aspects of GA disease pathogenesis may be more effective than monotherapy directed against isolated biochemical pathways.

The GATE study is the largest clinical trial to date that provides validated data regarding the rate of progression of geographic atrophy lesions. This study included a standardized follow-up protocol and software to quantify lesion size in a semi-automated manner. The standardized and prospective data acquisition of this clinical trial are of substantial value to contribute to the understanding of the pathophysiology and natural progression of GA. Additional analysis of data that may be of interest, including visual acuity loss data by baseline visual acuity, will be presented in future manuscripts. Subsequent trials on GA should take into consideration the limitations in the study design discussed, including limited understanding of the disease pathogenesis.

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